

THE
AMERICAN JOURNAL
OF THE
MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D.
EDITOR

RICHARD A. KERN, M.D.
ASSISTANT EDITOR

NEW SERIES

VOL. 201



LEA & FEBIGER
PHILADELPHIA

1941

LEA & FEBIGER
1941

PRINTED IN U. S. A.

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JANUARY, 1941

ORIGINAL ARTICLES.

CHLOROSIS. ESSENTIAL JUVENILE IRON DEFICIENCY
ANEMIA.

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WITHIN the variegated group of anemias, iron deficiency anemias claim their own distinctive and characteristic position. Our knowledge of etiology and pathogenesis in certain of these conditions, *e. g.*, hypochromic anemias in childhood and anemia due to chronic blood loss, is comparatively well developed; likewise has been confirmed and extended the clinical knowledge of simple achylic anemia, the disease first established as a clinical entity by Faber^{5b} about 30 years ago.

To chlorosis, formerly regarded as the prototype of hypochromic anemias, however, the reverse of the above applies. Nothing is heard of that disease; almost nothing is written about it and the few publications treat it most usually from a medico-historic angle. The diagnosis of chlorosis has disappeared from the annual reports of the hospitals, and today few physicians venture to make the diagnosis. Taken as characteristic of chlorosis is a hypochromic anemia occurring in young women, usually single, who have a normal gastric excretion, the anemia apparently being due to iron deficiency and responding to iron treatment.

When a disease such as chlorosis, known for centuries and formerly occurring to such an extent that it could be traced in popular literature and nowadays has ceased to occupy the human mind, it must, of course, primarily be due to the fact that chlorosis is not seen as frequently as formerly. This lowered incidence is undoubtedly caused by several, in part unknown, circumstances, one of which is the development of medical diagnostics; formerly the disease was not infrequently diagnosed in cases without any etiologic connection

NOTE.—In view of present uncertainties of postal communications abroad, it has not seemed desirable to the Editors to await further the author's proof corrections of this article.

with true chlorosis, these cases being in particular anemias due to hemorrhage in peptic ulcer, at that time of frequent occurrence in young women. Improved diagnosis alone cannot, however, explain the disappearance of chlorosis; a genuine decrease of frequency must have taken place during the last 30 to 40 years. This has, indeed, been substantiated by Cabot³ in the United States, later by Campbell⁴ in England and Bürger² in Germany. In Scandinavia, Schaudman¹⁵ showed the decreased incidence of chlorosis in Finland, and in Denmark, Hansen⁹ demonstrated that while in the years 1898 to 1903 from 9 to 17 cases of chlorosis were treated annually in the two medical departments of the Rigshospital in Copenhagen, only one single case was treated in the entire period from 1915 to 1920 in the same two departments.

Thus it is beyond any doubt that the incidence of diagnosed chlorosis has decreased pronouncedly. The cause, or better causes, of the decrease have on the other hand hardly as yet been established. The question to be discussed in this paper is whether a veritable disappearance of the disease has taken place, or whether cases of chlorosis do still occur, not being recognized and reported as such.

Judging from the Danish literature on chlorosis the former possibility seems to be the more likely; apart from the medico-historic monograph of Hansen⁹ a single clinical lecture by Gram^{7b} constitutes the entire Danish literature on the subject from the last 30 years. From other countries, and with certain usually very long intervals, however, contributions on chlorosis do still appear (Witts,¹⁷ Patek and Heath,¹³ Heilmeyer,¹⁰ suggesting that the disease has not altogether ceased to exist.

In Medical Department B of Frederiksberg Hospital has recently been treated a woman whose case history is of interest in the above mentioned discussion.

Case Reports. CASE 1.—Mrs. E. R., aged 27, in Dept. B, Jan. 24 to Feb. 19, 1940. History without interest until 1930 when she contracted rheumatic fever and, subsequently, endocarditis. The joint affections, however, rapidly subsided, and the heart affection has never since caused symptoms; she later bore 2 children, the last in the spring 1938. Now and then there have, however, been slight and transitory joint pains, never demanding any treatment. In 1931 the patient was treated in Medical Dept. II of the Copenhagen City Hospital for simple anemia (hematologic findings, Table I); iron therapy was highly effective. Menstruation always regular, of normal flow and duration. Never dyspeptic complaints, nor hematemeses, nor melena.

During the fall of 1939 the patient began to suffer from fatigue and lack of appetite, and had difficulty in managing her domestic affairs; increasing fatigue and slight joint pains caused her admission to the hospital.

Physical examination on admission revealed an anemic patient in moderate state of nutrition. No dyspnea, no edema. Stethoscopy of the heart showed slightly extended limits; a systolic murmur was heard. No other abnormal findings were observed. Temperature was normal, surface of the tongue was normal and there were no objective joint changes. Gynecologic examination showed normal conditions.

Special examinations: Urine: nothing abnormal. Wassermann reaction and gonococcus complement fixation test were both negative. Blood-pressure: 115/70. Sedimentation reaction (Westergren) 1 hr. 28 mm. → 3 mm. Electrocardiogram: nothing abnormal. Ewald test meal (1 hr.): 112 cc. free acid: 20 units, total acidity: 44 units. Feces: no blood (negative benzidine reaction). Radiologic examination of heart, lungs, stomach and duodenum showed normal conditions. Basal metabolism, -1. Ascorbic acid in serum: 0.80 mg. per 100 cc. Blood urea: 30 mg. per 100 cc. For blood counts see Table 1. Of 5560 white blood cells, 47% were neutrophils, 4% eosinophils, 3% monocytes and 46% lymphocytes. Daily reticulocyte counts Jan. 31 to Feb. 14: less than 1%. Sternal puncture showed slight augmentation of ripe erythroblasts and, of erythroid mitoses, as observed in simple anemias; nothing else abnormal was found. After Jan. 30 the patient was treated with ferrous tartrate 0.5 gm. 3 times daily.

TABLE 1.—BLOOD COUNTS IN CASE 1.

	Hb (%).	R. B. C. (mills. per c.mm.).	Color index.	W. B. C. (per c.mm.).
October 9, 1931	43	2.50	0.9	7300
November 11, 1931	74			
January 29, 1940	51	5.06	0.5	5560
February 5, 1940	65	5.99	0.5	
February 19, 1940	71	5.64	0.6	
February 23, 1940	79	5.65	0.7	

Discussion and Diagnosis. The patient exhibited the typical picture of a moderate hypochromic anemia; no anemia producing factor could, however, be substantiated. Neither manifest nor occult hemorrhage was or had been present; she had no other organic disease of significance, and no metabolic or avitaminotic disorder; acid secretion in the stomach was normal. A distinctive feature was in particular the normal red blood cell count in spite of a considerably lowered hemoglobin percentage, *i. e.*, a pronounced hypochromia; this feature especially called attention to the diagnosis of chlorosis, this diagnosis being further confirmed by the want of any intrinsic or extrinsic cause of anemia.

Against the diagnosis really only the age of the patient counted, but probably the case may be conceived as "*late chlorosis*" (Naegeli,¹² Witts¹⁷); it may, however, be still more correct to consider the patient's anemia back in 1931 as her first attack of chlorosis; consequently the present attack may be conceived as *recurring chlorosis*; recurrences are not rare in chlorosis; according to Cabot³ they occur in 50% of all cases. Regardless of the two concepts mentioned the patient undoubtedly suffered from chlorosis or, a better term, *essential juvenile iron deficiency anemia*.

Chlorosis in Dept. B, Frederiksberg Hospital, Copenhagen, 1930 to 1940. The case reported sustained the surmise that chlorosis still occurs in Denmark, but so rarely that it most frequently does not get recognized and diagnosed under its proper name. Endeavoring to trace similar cases that might have occurred in the course of time, I have searched the case records of all patients treated in Department B for simple anemia since Jan. 1, 1930. My diagnostic criteria

have been: hypochromic anemia in adults, not being due to blood loss or infection, and the acid secretion of the stomach being unimpaired.

It promptly appeared that anemia cases of that sort were extremely rare. The above mentioned case excepted, only 5 cases were found, all female, in spite of the fact that during the same 10 years a total of 77 cases of simple anemia were treated in the Department, the major part of these being either anemias due to chronic blood loss or simple achylic anemias.

The number collected is too restricted to convey any information on the frequency of chlorosis; for the sake of comparison, however, it may be mentioned that Witts¹⁷ using the criteria applied here found 18 cases of chlorosis in Guy's Hospital, London, during 9 years; of these 18 cases, all female, only 5 were less than 21 years of age. Accordingly, the numbers from Frederiksberg Hospital, Copenhagen, and Guy's Hospital, London, are within the same order of quantity. The remaining 5 case reports shall be briefly recorded in the following.

CASE 2.—Miss R. R. S., hair-dresser, aged 19, in hospital Jan. 26 to Feb. 23, 1939. No previous illness. During the year preceding admission she suffered from fatigue, vertigo, faints, menstrual disorder, lack of appetite, a few vomitings, and loss of weight; furthermore dyspnea on exertion and palpitation. Physical examination revealed nothing but anemia (see Table 3). Sedimentation reaction (1 hr.) 7 mm., Ewald test meal (1 hr.) 114 cc., free acid, 25, total acid, 58.

CASE 3.—Miss A. C., housemaid, aged 29, in hospital Oct. 18 to Nov. 11, 1937. No previous illness. For 2 weeks suffered from fatigue with headaches, gastric distress, lack of appetite and palpitation. Menstruation normal. Physical examination, nothing abnormal except anemia (see Table 3). Sedimentation reaction, 2 mm. Ewald test meal, 100 cc., free acid, 40, total acid, 75.

CASE 4.—Miss E. A., book-keeper, aged 35, in hospital Aug. 27 to Sept. 15, 1934. No previous illness, but for some time gastric distress; for 6 months preceding admission increasing fatigue; no other complaints. Menstruation always normal. Physical examination, anemia (see Table 3), otherwise nothing abnormal. Ascorbic acid in serum, 0.50 mg. per 100 cc. Ewald test meal, 99 cc., free acid, 20, total acid, 61.

CASE 5.—Miss A. M. L., housemaid, aged 22, in hospital Feb. 22 to March 24, 1934. No previous illness, but always "anemic" and "dyspeptic." For 2 to 3 months increasing fatigue with headaches, vertigo, tinkling in the ears, gastric distress, nausea, want of appetite, and loss of weight; for 1 month dyspnea on exertion and palpitation. Menstruation, always severe molimina, otherwise normal. Physical examination, anemia excepted (see Table 3), nothing abnormal. Sedimentation reaction, 9 mm. Ewald test meal, 129 cc., free acid, 22, total acid, 87.

CASE 6.—Miss A. H. B., unemployed, aged 21, in hospital Jan. 25 to Feb. 12, 1931. Sickly for a couple of years, but no other previous illness; suffered from increasing fatigue, lack of appetite, and loss of weight; furthermore headaches and vertigo. Menstruation normal. Physical examination, anemic (see Table 3) and somewhat emaciated. Sedimentation reaction, 4 mm. Ewald test meal, 47 cc., free acid, 46, total acid, 80.

Sex Incidence, Age and Occupation. As will be noted all 6 patients are female, this being in conformity with general experience;

chlorosis has always been a disease occurring exclusively in females, exactly like simple achylic anemia. Iron deficiency anemia occurring in males will practically always be due to a persisting or recently subsided hemorrhage. The age distribution of the patients appears in Table 2.

TABLE 2.—AGE DISTRIBUTION OF THE PATIENTS.

Years.	No. of patients.
Under 20	1
20 to 24	2
25 to 29	2
Over 29	1

If it is allowable to draw any conclusion at all from the age distribution of a material limited to 6 patients, the age distribution observed here is higher than elsewhere indicated. Thus out of Campbell's⁴ 153 patients only 14 were more than 25 years of age, and Cabot³ reports that 94% of his cases occurred in the years from 15 to 30. Stockman¹⁶ found as many as 65% of his patients to be between 15 and 20 years of age. The above mentioned material of Witts,¹⁷ however, corresponds as to the age distribution fairly well to the one reported here.

Even if only half of our patients conform to the classical demands as to age, it is probably only in the single case of the patient aged 35 (Case 4) that the diagnosis of chlorosis would not have been made 40 to 50 years ago; it would, however, be an artificial distinction if this patient, solely because of her age, were separated from the remaining ones, when history and hematologic findings, as will be shown later, show a close etiologic and pathogenetic relation to them.

As to the occupation of the patients, it is at once striking that 5 are single and solitary women, and that all of the 6 originate from a modest social level. In the case of the only married woman (Case 1) the disease, however, is supposed to be a recurrence of a previous attack, occurring at a time when she, too, was single and solitary.

Hematologic Findings. In Table 3 are put down the hematologic findings before treatment. It clearly shows the pronouncedly hypochromic anemia present in all of the cases; characteristic findings are especially observed in Cases 1, 2 and 6, where the red blood cell counts are above the normal in spite of a definitely lowered hemoglobin percentage. This circumstance seems to be specific of chlorosis and has been observed already at an early stage. As an example may be mentioned that of the 7 cases of chlorosis recorded in Gram's⁷ monograph, from 1883 only 4 had red blood cell counts from 4,600,000 to 5,200,000 although at the same time is noted that the patients were pronouncedly anemic. In a similar way the lowest blood cell count in the cases published by Cabot³ is 4,050,000.

TABLE 3.—HEMATOLOGIC FINDINGS BEFORE TREATMENT.

Case.	Age.	Hb. (%).	R. B. C. (mills. per c.mm.).	Color index.	W. B. C.	Lympho- cytes (%).
1	28	51	5.06	0.5	5560	46
2	19	53	5.28	0.5	8880	40
3	29	46	2.99	0.8	4560	38
4	35	45	4.26	0.5	4920	24
5	22	49	3.92	0.6	4880	29
6	21	62	5.34	0.6	5000	24

The white blood cell counts ranged within normal limits, and only in 3 patients (Cases 1, 2 and 3) was slight relative lymphocytosis observed. The sedimentation reaction (Westergren) was temporarily increased in Case 1, in the remaining 5 patients it was normal. In Cases 1 and 3 ascorbic acid determination in serum was carried out and normal values obtained. Finally, in Case 1 daily reticulocyte counts were performed over a period of 2 weeks; counts ranging around 1% were noted, this being in conformity with the findings in 2 cases recently published by Heilmeyer.¹⁰

Clinical Symptoms. As long as chlorosis has been known it has been connected with menstrual disturbances, these having been regarded sometimes as a symptom of the disease, sometimes as its cause. The same applies to the dyspeptic complaints frequently present, and most usually in the form of gastric distress, want of appetite, and constipation, but also, and especially in former times, peptic ulcer and gastric hemorrhage ("gastrostaxis" Hale-White⁸).

It is, of course, obvious that menorrhagia and hematemesis may cause a post-hemorrhagic hypochromic anemia, but cases of that sort cannot be regarded as chlorosis. The elucidation of this circumstance is exactly one of the known causes of the decreased incidence of chlorosis. The remaining symptoms encountered in the literature, *viz.*, fatigue, dyspnea, vertigo, fainting, and eventually, venous thrombosis are ordinary anemic signs and not at all distinctive of chlorosis.

TABLE 4.—CLINICAL SYMPTOMS.

Symptoms.	Cases.						Total.
	1.	2.	3.	4.	5.	6.	
Fatigue	x	x	x	x	x	x	6
Lack of appetite . . .	x	x	x	..	x	x	5
Gastric distress	x	x	x	x	..	4
Headaches	x	x	..	x	x	4
Vertigo	x	x	x	3
Palpitation	x	x	..	x	..	3
Dyspnea	x	x	..	2
Faints	x	x	..	2
Constipation	x	x	2
Menstrual disorder	x	x	..	2

In Table 4 are collected the clinical symptoms exhibited by the 6 patients here mentioned. It will be seen that the main symptom has been fatigue, all 6 patients having suffered from it. Five patients complained of dyspeptic troubles such as want of appetite and gastric

distress; headaches, vertigo and slight cardial troubles were noted by half of the patients. Strangely enough menstrual disturbances have been present in 2 cases only. It must repeatedly be emphasized that in spite of dyspeptic complaints gastric acidity was normal in all 6 patients and no blood could be detected in the feces.

Cabot³ observed dyspnea in 80% of his patients and edema of the feet in 60%; Campbell⁴ gives the corresponding numbers as 90% and 40%. Only 3 of these patients complained of dyspnea, and edema was found in none. Cardial complaints, however, are hardly specific of chlorosis, but merely an expression of the degree of anemia.

The clinical picture, offered by our patients, differs in a few respects from classical chlorosis and so does the age distribution of the patients. The majority of earlier authors agree that chlorosis occurs simultaneous with or few years after puberty; this has, however, been the case in only one of these patients (Case 2); in the remaining cases the disease did not develop until several years after puberty. It might, therefore, be more correct to describe these patients as suffering from *essential juvenile iron deficiency anemia* instead of chlorosis. It is no doubt the same disease, the only difference being that it does not nowadays occur preferentially in quite young women. On the other hand, juvenile iron deficiency anemia must be kept definitely distinct from another clinical syndrome: simple achylic anemia, the latter occurring at a later age, and the presence of gastric achylia suggesting a different etiology.

Etiology. Pathogenesis in chlorosis is fairly well elucidated inasmuch as hematologic findings and therapeutic response prove the anemia to be due to iron deficiency. Etiologically, however, little has been achieved and it is still obscure why the disease develops. Hence the countless theories of the etiology of chlorosis, advanced during the course of years, which fact can only be regarded as a valid expression of our ignorance.

From early times attention has been paid to the menstrual disturbances and the gastro-intestinal complaints, but anemia due to menorrhagia or gastric hemorrhage would not today be termed chlorosis. Neither would the dislocations of the stomach, likewise advanced as an etiologic factor, today be given the same importance as formerly. The purely speculative theories of Ashwell¹ and Rokitsansky,¹⁴ suggesting anomalies of evolution and stricture of the aorta as the cause of chlorosis would no more today be ascribed etiologic significance.

In the medico-historic monograph of Hansen⁹ is shown a conjunction in time between the incidence of chlorosis and the female use of stays, but a causal conjunction between these two factors is not definitely proved.

In 4 cases of chlorosis, published by Patek and Heath,¹³ the authors were able to substantiate a dietary iron deficiency; they believe, therefore, that increased growth during puberty and onset of men-

stration, combined with dietary deficiency form the cause of chlorosis. Heilmeyer,¹⁰ too, ascribes great import to nutrition deficient in iron, but emphasizes furthermore the significance of lowered iron absorption. Absorption of iron does seem to be lowered, as shown by his 2 cases of chlorosis, both of which exhibited decreased serum iron.

It is, accordingly, improbable that one single factor causes chlorosis; the condition is sooner caused by a combination of factors, most likely chiefly of general hygienic and nutritional nature. Adopting this concept, however, we have hardly made progress beyond early clinical experience; as early as in 1896, *e. g.*, Faber⁶ wrote: "It is an undisputable fact that chlorosis develops especially in young girls leading an indoor life in dark or semidark rooms."

A material as limited as the one here recorded cannot, of course, yield any important contribution to the etiology of chlorosis in general; several circumstances, however, are striking to a degree that they are worth mentioning. Thus it is characteristic that 5 of the 6 patients here mentioned were single women, all living in economically and nutritionally very modest environs; the sixth patient (Case 1) was married, but she had, as already mentioned, suffered from her first attack of chlorosis at the age of 18, at a time when she, too, was single.

By occupation 4 were doing domestic work, 1 was a hair-dresser and 1 a book-keeper. No information is available as to any special dietary deficiency, but the social entourage of the patients was of a sort that renders a nutritional deficiency probable; they were, furthermore, all thin, a few of them almost emaciated women, weighing from 49.5 to 65.2 kg., and it is noticeable that 5 patients gained from 0.8 to 1.7 kg. in weight during their stay in hospital, in spite of this being only of 3 to 4 weeks' duration. In 1 patient, however (Case 2), there was a loss of weight amounting to 0.8 kg. Without drawing any certain conclusion from these circumstances it may be suggested that all of these women prior to admission into the hospital had been living on a diet, at any rate quantitatively insufficient.

Another fact of interest is the point of time of the admissions; it appears that 4 of the 6 patients were admitted into hospital within the 30-day period from Jan. 23 to Feb. 22; the 2 remaining patients were admitted in August and October, respectively. It may, of course, be entirely accidental that the majority of admissions were in the darkest season of the year, but confronted with the facts mentioned it supports the suggestion of the etiologic import of hygienic factors. Previous authors, *e. g.*, Faber,^{6a} have already called attention to the importance of light, or rather darkness, for the development of chlorosis. A true avitaminosis, however, seems to be out of question; vitamin C avitaminosis, occasionally causing hypochromic anemia (Mettier, Minot and Townsend¹¹) would be most probable, but in both cases (Cases 1 and 3) in which determi-

nations of ascorbic acid in serum were carried out normal values were obtained.

These cases of chlorosis, developing in solitary women whose diets most likely were quantitatively insufficient, and occurring at a season when foods in general are thought to be qualitatively deficient sustain, therefore, the supposition that nutritional and general hygienic factors play an important rôle in the development of chlorosis; it may, furthermore, be possible that lowered iron absorption is contributive, but in these women no information of any dietary iron deficiency is available. No other causes of anemia can be suggested in these patients; it must especially be observed that all of them had normal gastric function, and none showed signs of any external or internal hemorrhage.

The cases recorded here do not, unfortunately, offer any explanation of the lowered incidence of chlorosis. Presumably it is the changed conditions of life of the young women that constitute the true cause of the disappearance of the disease from the age where it was formerly most common.

Treatment.—The treatment will be but briefly dealt with. In all of the cases an energetic iron therapy caused within a short time, a considerable rise of the hemoglobin percentage (Table 5).

TABLE 5.—RESULTS OF IRON TREATMENT.

Case.	Hemoglobin (%).		Period of observation, days.
	Before.	After.	
1	51	79	25
2	53	81	17
3	46	83	17
4	45	60	11
5	49	75	27
6	62	70	9

As to the preparations applied, 2 patients (Cases 1 and 2) were given ferrous tartrate 0.5 gm. 3 times daily; the remaining 4 were treated with reduced iron 0.5 gm. 3 times daily. Unfortunately the period of observation has in certain cases (Cases 4 and 6) been too limited, but even within the restricted period the effect of iron therapy is evident.

In Case 1 (see Table 1) is observed the effect of iron on the red blood cells, the number of which in 1 week rose from 5,060,000 to 5,990,000; this increase to values above the normal is, according to Castle and Minot,⁵ distinctive of chlorosis. The same feature was observed in Case 4, where the red blood cells subsequent to 11 days' iron therapy rose from 4,260,000 to 5,690,000. Unfortunately the case records of the remaining patients do not yield any information of this fact, important also in diagnostic respect.

In 1 patient only (Case 1) the reticulocytes were counted; no response after iron therapy was observed. This is the more curious as reticulocyte responses subsequent to iron administration are

noted both in anemia due to chronic blood loss and in simple achylic anemia. Concerning reticulocytes in chlorosis nothing much is known, however, and from a single case generally valid conclusions cannot be drawn, of course.

The results of treatment in these cases are in perfect accordance with old clinical experience; no explanation is given, however, of the curious fact, why it is necessary to prescribe iron in such heavy amounts to cover a deficiency less than 1 day's administration.

Summary. Six cases of chlorosis in young women are reported, these being the only cases observed during the last 10 years in Medical Dept. B, Frederiksberg Hospital, Copenhagen. The hematologic findings, the clinical picture and the etiology are discussed. In certain respects the disease as mentioned here differs from classical chlorosis; this concerns especially the age distribution of the patients, which is somewhat higher than that found in earlier materials; likewise, menstrual disturbances seem to be more rare than generally reported. As to the etiology, two facts are of importance; first, all of the 6 patients are from an economically and socially modest level, the evidence suggesting that their diets have been quantitatively insufficient; second, two-thirds of these admissions occurred in the darkest season of the year; within the space of 30 days toward the end of January—this suggests a qualitative dietary deficiency. All patients responded well to iron treatment; even when starting with normal red blood cell counts a rise of 1,000,000 was observed within a week, the diagnostic import of this feature is emphasized. Finally, instead of the name of chlorosis the term *essential juvenile iron deficiency anemia* is suggested.

Conclusions. Based on the cases recorded here it may be permissible to conclude that chlorosis has not, as generally assumed, entirely disappeared, but that it does still occur, even if with comparative infrequency. The diagnostic criteria remain the same as ever: hypochromic iron deficiency anemia without any demonstrable cause, occurring in young women with a normal gastric function. The disease, however, nowadays seems to be most common in women of a later age than formerly. As the term chlorosis always preferentially has covered an anemic condition in young girls shortly after puberty, it might be better instead of chlorosis to use the denomination *essential juvenile iron deficiency anemia*. In this way, furthermore, the disease is kept distinct from another condition, simple achylic anemia; for even if the two diseases show a certain pathogenetic relation, they must still be regarded as definitely separate entities.

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THE EFFECTS OF FOOD COMBINATIONS UPON LEUKOPENIC INDEX DETERMINATIONS AND UPON BODY TEMPERATURE.

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THE leukopenic index was introduced into medicine in 1934 by Vaughan^{16a,b} and consists of a series of postprandial total leukocyte counts made at specified intervals after first obtaining the fasting count. The test was a sequel to the work of Widai, Abrami and Iancovescu,¹⁷ who in 1920 proposed the colloidoclastic crisis test for liver function, which consisted in the administration of 200 cc. of milk to an individual in the fasting state. A positive reaction indicative of hepatic dysfunction was evidenced by a falling curve of total leukocyte counts, falling blood pressure and a prolonged clotting time. At the time this test was proposed it was generally believed that the ingestion of food is followed by a leukocytosis.

In the performance of the hemoclastic crisis test, Vaughan concluded that it was not reliable as a test for liver function. However, he did see patients during its performance in which milk caused a fall in the total white count. It occurred to him that if a leukopenic response follows the ingestion of milk to one allergic thereto and if such is an allergic response rather than one due to hepatic insufficiency, it is probable that a similar reaction will follow the ingestion of other foods to which one is allergic also. If such reasoning were correct, a new test could be introduced into medicine to supplement the skin tests in the diagnosis of food allergy.

In Vaughan's original work the test was applied by having the patient report to the office in the morning in a fasting state. Two fasting counts were made at 10-minute intervals. The patient then ate an average portion of the food to be tested. Subsequent counts were made at 15-minute intervals for 1 hour. A final count

was made at the end of $1\frac{1}{2}$ hours. The same pipette and counting chamber were used for each count on a given patient. A fluctuation of 2000 cells in the total count was allowed as normal. A drop of more than 1000 cells below the mean of the two fasting counts was regarded as of possible significance. The character of the entire curve was considered in the interpretation. Through the use of the bromallergram or food-allergy-graph, foods were classified into three groups according to their leukocyte response. Foods in Group 1 caused no drop in the white count and were considered to be in positive balance and to produce no symptoms. Foods in Group 2 caused a sharp drop of more than 1000 cells and were considered to be in negative balance and to be definitely allergenic. Foods in Group 3 caused a slight drop in cells, less than 1000, which was considered to be a borderline reaction. Such foods were deemed capable of producing or not producing symptoms. The individual was considered to be in a balanced allergic state in regard to foods in this group.

Subsequent refinement of technique in performing the leukopenic index was proposed by Vaughan, Rinkel,^{10a,b,11} Gay⁵ and others. The test as run today is to have the patient report to the office at 9 A.M. in a fasting state of at least 12 hours. After a rest of 30 minutes, one or two fasting counts are made at 10-minute intervals. Five minutes are then allowed for the patient to eat an average portion of the food to be tested, and subsequent counts are made at 15-minute intervals for 1 hour. Some investigators apply the test at 20-minute intervals for 1 hour or at 30-minute intervals for $1\frac{1}{2}$ hours. The general feeling is that the patient should sit quietly during the test and refrain from talking and smoking. No condiments are eaten with the food, which is heated to body temperature as nearly as possible. Best results are claimed if the patient presents himself in a calm, even state of mind, as free from worry and emotional influences as possible. Except in the intractable allergies, the food to be tested should be eaten for several days before the test is made. The same pipette and counting chamber are used for each count on a given patient. The pipette is shaken for 3 minutes and the cells allowed to settle 5 minutes before the counting is begun. From 8 to 32 sq. mm. of cells are counted at each count in different clinics.

Following Vaughan's investigations the work of Rinkel contributes greatly in the interpretation of the leukopenic index. He uses 3 counts made at 20-minute intervals and feels that the increase or decrease in total counts are not as significant as the type of curve that is visualized by means of a graph. Such curves are classified into three groups. In Group 1 is the compatible curve which is defined as "one having 2 successive increases in the total white count, the first of which is greater than the known error in counting, the second being more than 1000 cells above the initial

count, and the count at the end of the hour being definitely greater than the beginning one." In Rinkel's and Gay's¹¹ combined experience of 5000 tests, they did not find an exception to this definition of a compatible curve. Foods producing curves of this type are considered to be non-allergenic and to cause no symptoms. Such foods may be compared to those in Vaughan's positive balance group, which do not cause any drop in the white cells. The compatible curve is spoken of also as a negative curve and the leukopenic index is said to be negative. In Group 2 is the indeterminate curve which does not exceed 1000 cells above or below the fasting count. Foods producing curves of this type may or may not cause symptoms. Such foods may be compared with those in Vaughan's negative balance group which cause a drop of less than 1000 cells. In Group 3 is the incompatible curve in which the drop in the leukocytes exceeds 1000 cells. Foods producing curves of this type are considered to be definitely allergenic and to cause symptoms in 90% of cases. Such foods may be compared to those in Vaughan's negative balance group which cause a sharp drop of more than 1000 cells. The incompatible curve is spoken of also as a positive curve and the leukopenic index is said to be positive.

Rinkel believes that the test is not constant always for the same food and that it may vary from a positive to a negative phase. He feels that certain individuals with intractable allergy do not have a negative leukopenic index to any food and, if they should have, they cannot maintain it after the ingestion of a given food repeatedly. This inability to maintain tolerance to a food and the almost universal sensitization to foods in intractable allergy presents an important problem in diagnosis and therapy. Such reactions suggest a logical explanation for the cause of these intractable cases. The protective mechanism has broken down almost completely, or has become ineffective. That the normal tendency is to recover is indicated by the fact that with the omission of foods which give positive leukopenic indices the positive reaction tends to become negative again.

The clinical studies of a large group of other investigators show that the value of the leukopenic index as a diagnostic aid in allergy is in a controversial state at present. While the majority of writers feel that the test is of value clinically,^{1,3,6,8,9} others feel that the test is not of proved value.

Plan of Present Investigation. In the present study the author presents the work as a pictorial study of investigations which began in October, 1937, and ended in October, 1939. He does not seek to confirm or refute the value of the leukopenic index as a diagnostic aid in food allergy primarily. Rather, through a series of tables and graphs he wishes to show the response of the leukocytes obtained by this test to his ingestion of 101 individual foods and to 42 combinations of foods. His interest in the problem has its basis

in a striking family history of allergic disturbances. The father, who is 70 years of age, has had chronic bronchitis for 35 years. The mother, who is also 70, has had chronic indigestion for over 40 years. One sister has had an almost intractable bronchial asthma for 30 years. Another sister has hay fever. Two brothers suffer with an irritable type of colon, and the author suffered for 25 years with chronic sinusitis and an irritable colon, more severe than in his brothers. To understand better the allergic manifestations in his family, as well as those apparently in himself, the author felt that he was a fit subject upon whom to employ this test. It was his impression that if the ingestion of food can influence definitely the manner of the response of the leukocytes, that certain types of responses to individual foods and to combinations of foods could be demonstrated. He will make his meaning clear by asking 4 hypothetical questions:

1. If the ingestion of one food produces a leukocytosis and the ingestion of another food produces a leukocytosis, will the simultaneous ingestion of two or more such foods also produce a leukocytosis?

2. If the ingestion of one food produces a leukopenia and the ingestion of another food produces a leukopenia, will the simultaneous ingestion of two or more such foods also produce a leukopenia?

3. If the ingestion of one food does not increase or decrease the leukocytes to more than 1000 cells above or below the fasting count, and the ingestion of another food acts similarly, will the simultaneous ingestion of two or more such foods act likewise?

4. The fourth and most critical test of the effect of ingestion of food upon the leukocyte response would be, if the ingestion of one food produces a leukocytosis and the ingestion of another food produces a leukopenia, will the simultaneous ingestion of two such foods produce a neutralizing or composite response of their individual leukocyte responses?

To determine if such responses of the leukocytes could be demonstrated, essentially all of the known foods were tested. In order that every detail of the investigation might be known and controlled carefully, the author elected to do the counts himself, thereby making the technical aspect of the study constant for each test.

Technique and Method. Each individual test and each combination test was done on a separate day, beginning at 9 A.M. No food was eaten for 12 hours preceding the tests. On the morning of each test, the author omitted brushing his teeth to avoid the effects of dentifrices in his mouth, and no water was taken until after the completion of the test. Care was taken to keep in an even state of mind and to be free from emotional influence and worry. A rest of 30 minutes was employed before beginning each test. To simplify the procedure, a single fasting count was made. Throughout the study, the same pipette and counting chamber were used for each test. Sixteen square millimeters of cells were counted at each count. Blood was obtained from the tip of the finger by a sharp needle, inserted through a rubber stopper, so that the depth of the incision would be the same. The first 3 drops of blood were discarded. A different finger was used for each

test. A 0.5% solution of glacial acetic acid, in distilled water, was employed as diluting fluid. The pipette was shaken for 3 minutes in 2 planes at right angles to each other to insure proper mixing. The first 3 drops from the pipette were discarded. Two chambers were filled uniformly as possible and the cells allowed to settle 5 minutes. During the 5 minutes, in which the cells were settling, the food to be tested was eaten. Care was taken to have the food heated to body temperature as nearly as possible. No water or condiments were allowed except in the first few tests, in which salt and water were taken. Three postprandial counts were made at 30-minute intervals. After 40 tests were run, determinations of body temperature were made, preceding each fasting and postprandial count. A certified clinical thermometer was used for this purpose. Except for the first 15 tests, all remaining tests were performed in the same room and at the same desk. The author cleaned the pipette and counting chamber after each count. To do this he walked 15 feet each way to a laboratory sink. Thus, there was introduced into the investigation a moderate amount of mental and physical activity in performing the counts and in cleaning the pipette and counting chamber. These factors were operative throughout the investigation, and were constant in the part they played towards influencing the results.

The author supervised the selection and preparation of each food and combination of foods. Each food was eaten in its natural state, if possible. If cooking was necessary the same degree was attempted for each food. Care was taken that all utensils were cleaned carefully. Approximately the same quantity of food was eaten for each combination test as was eaten during the test for each individual food. An average testing quantity was three-fourths cupful. Care was exercised to insure that part of the same identical food was used for both the individual test and the combination test. For instance, in the combination test for cantaloupe and watermelon, the same cantaloupe and watermelon were used as were used in the individual tests on these foods. In the combination test for rice and sweet potato, enough of the same rice and the same sweet potato were prepared to run the individual tests and their combination test. Where a special kind of fruit or berry was tested, enough of that particular variety was purchased to insure that the individual tests and the combination test be run with that same variety. Such uniformity was planned throughout the investigation. A portion of the same food as was used in each individual test and combination test was eaten at least once a day for 5 days before the tests were made.

In order that the effects of alcohol and ether might be determined, inasmuch as they were used to clean the pipette and counting chamber before each count, indices were run on these substances. During the tests, care was taken not to aspirate the pipette to clean it. A suction bulb was used to dry the pipette. In such manner no ether or alcohol became a contaminant by getting into the author's mouth. However, the factor of inhalation of ether and alcohol, in vapor form, was present throughout the tests in a very minimal degree.

In Figures 1 to 7 (Graphs 1 to 84) the serial counts with each food, and combination of foods, are depicted in the form of curves. These curves are plotted so that a variation of 100 cells, above or below the fasting count, can be seen. The ordinates of each graph represent an increase or decrease in the postprandial counts above or below the fasting count which is represented at the zero position. The abscissæ represent time elements of each test, expressed in intervals of 30, 60, and 90 minutes. The center of interest in each graph is the space delineated by the two heavy lines drawn hori-

zonally at the zero and minus 1000 positions. This space denoting a decrease of as much as 1000 cells in any of the 3 postprandial

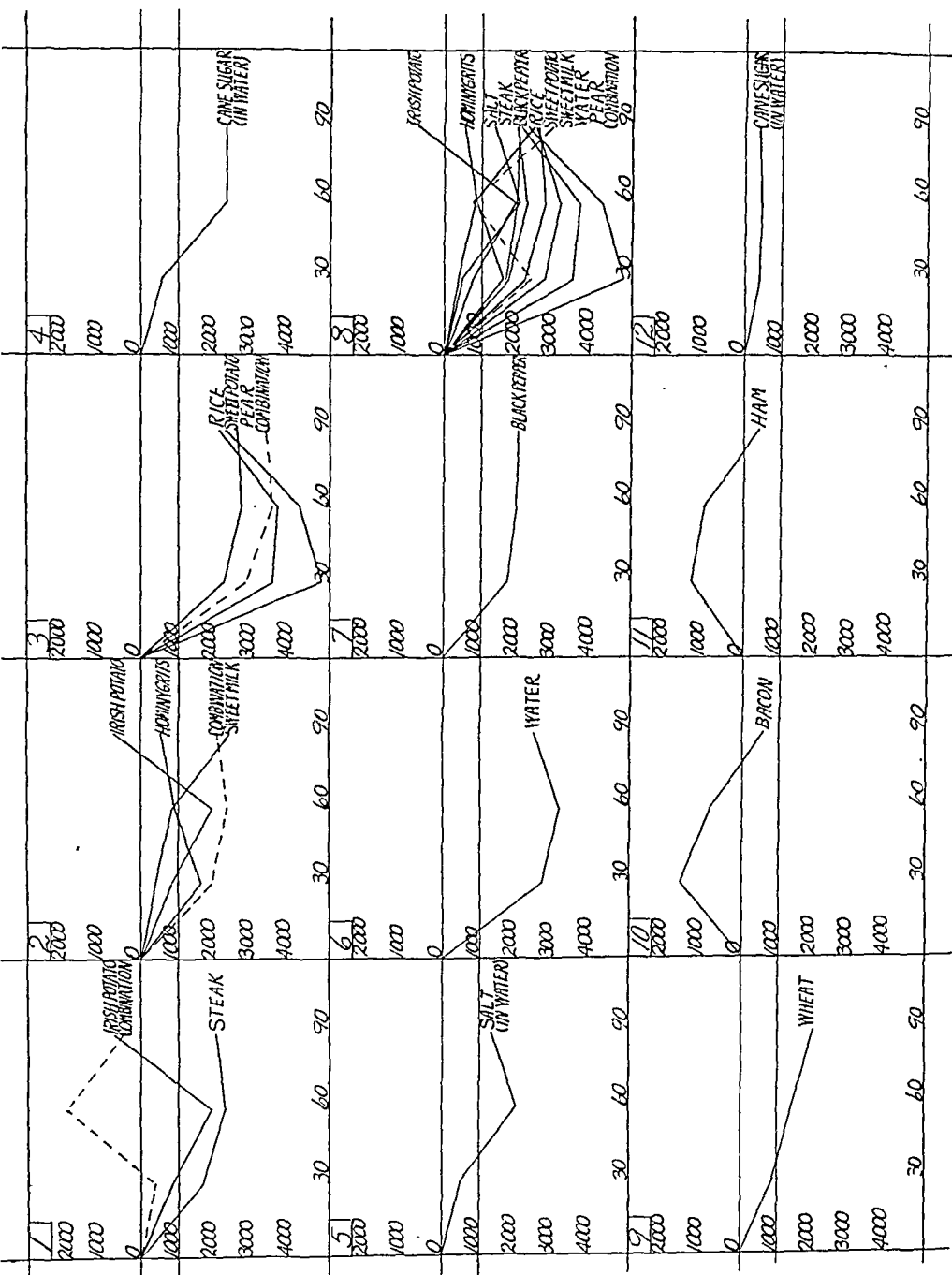
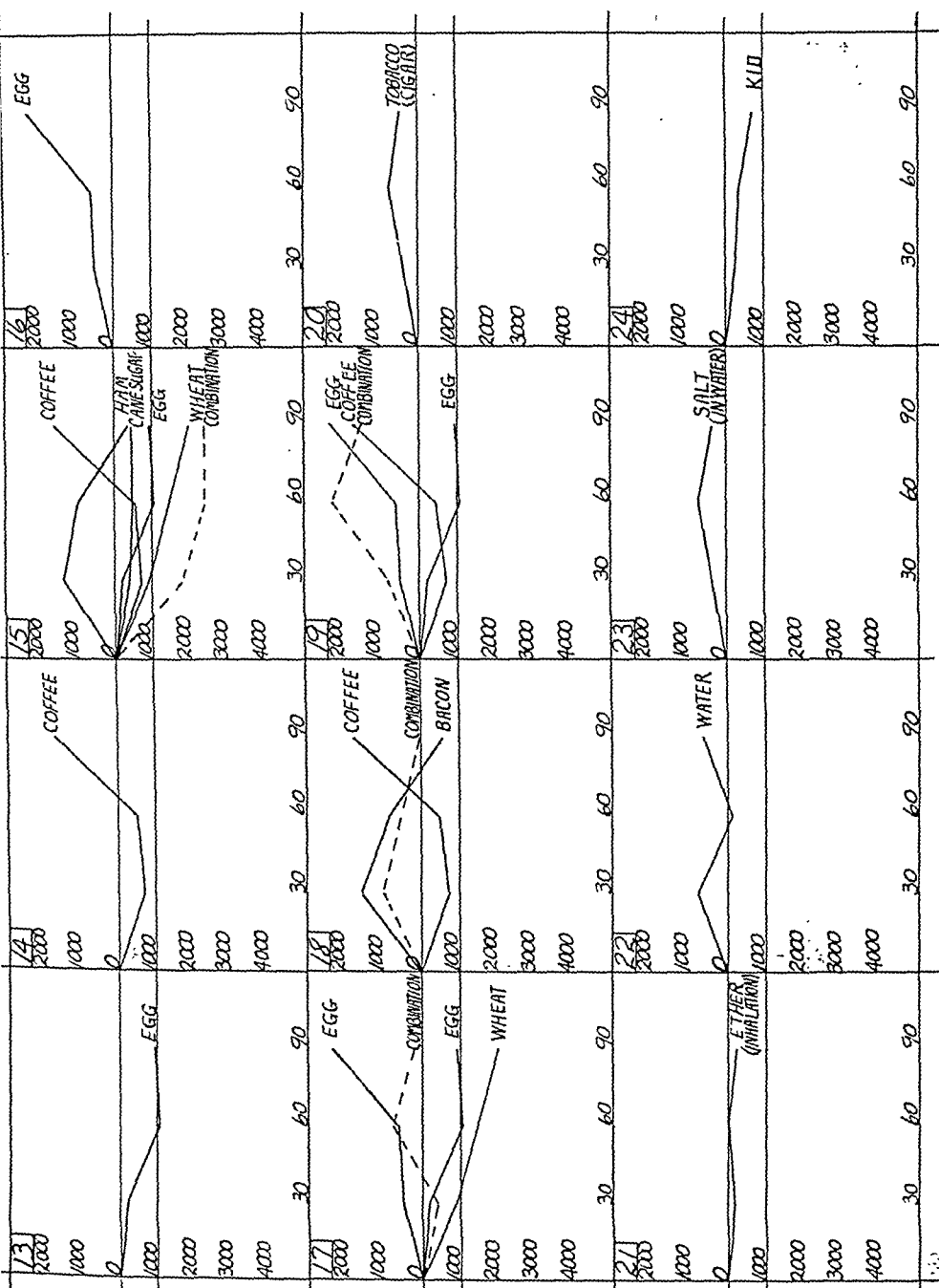


Fig. 1.—Curves of individual foods and combinations of foods (Graphs 1 to 12).

counts identifies each food that produces a leukopenia, as great as 1000 cells. The respective curves fall into 3 positions in regard to

this space; those that lie above the plus 1000 position of the ordinates, at one or more points; those that lie between the plus 1000



and the minus 1000 positions, at all points; and those that lie below the minus 1000 position, at one or more points.

In each graph the leukocyte response to the individual food is represented by the unbroken line. Such a line, designated by the

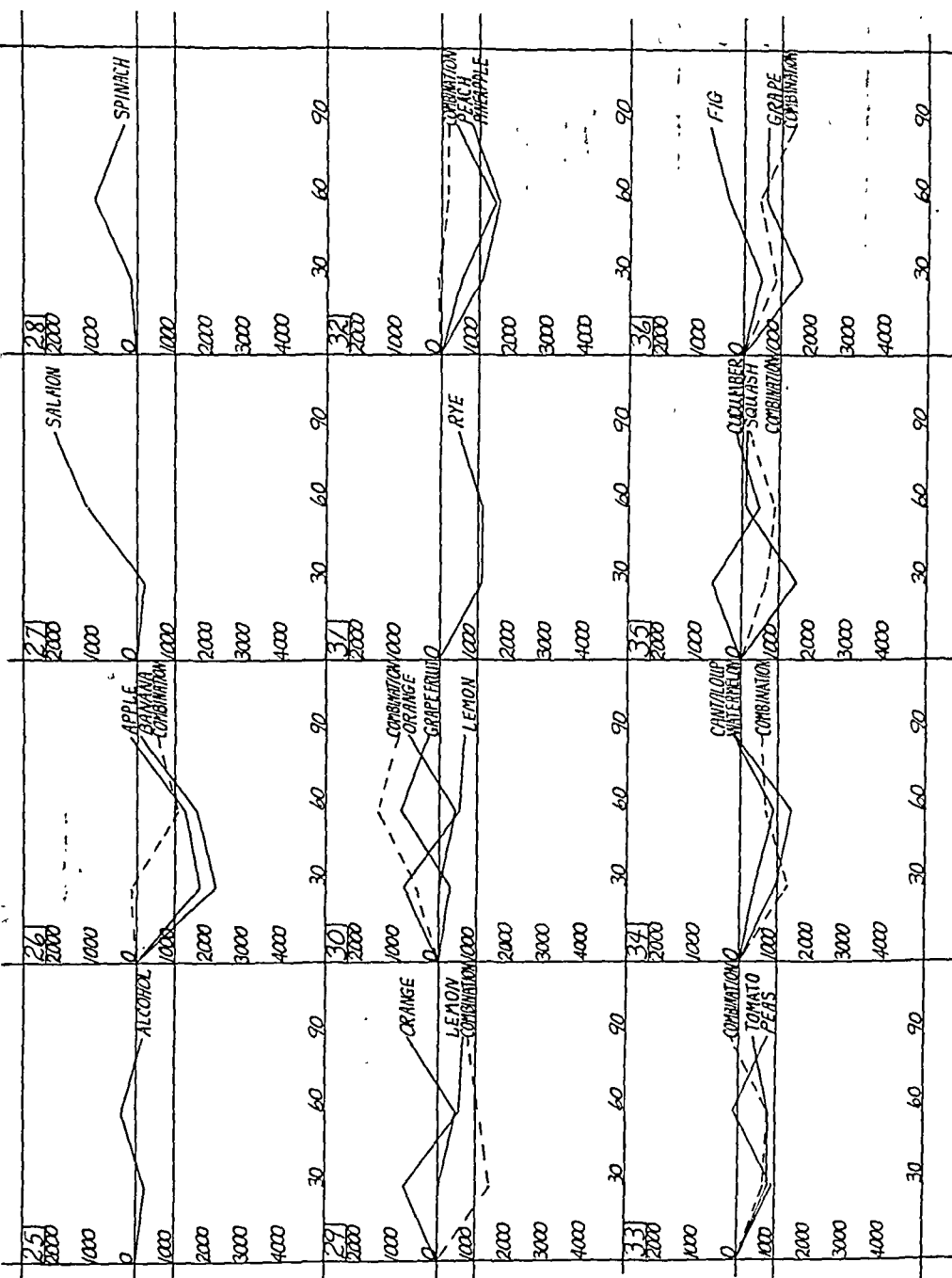


FIG. 3.—Curves of individual foods and combinations of foods (Graphs 25 to 36).

name of the respective food at the end of it, represents the test for that food as made on the date listed in Table 1. The leukocyte response to the combination of foods is represented by the broken

line and represents the simultaneous ingestion of all foods seen in that graph on the date, listed in Table 2. The combination tests

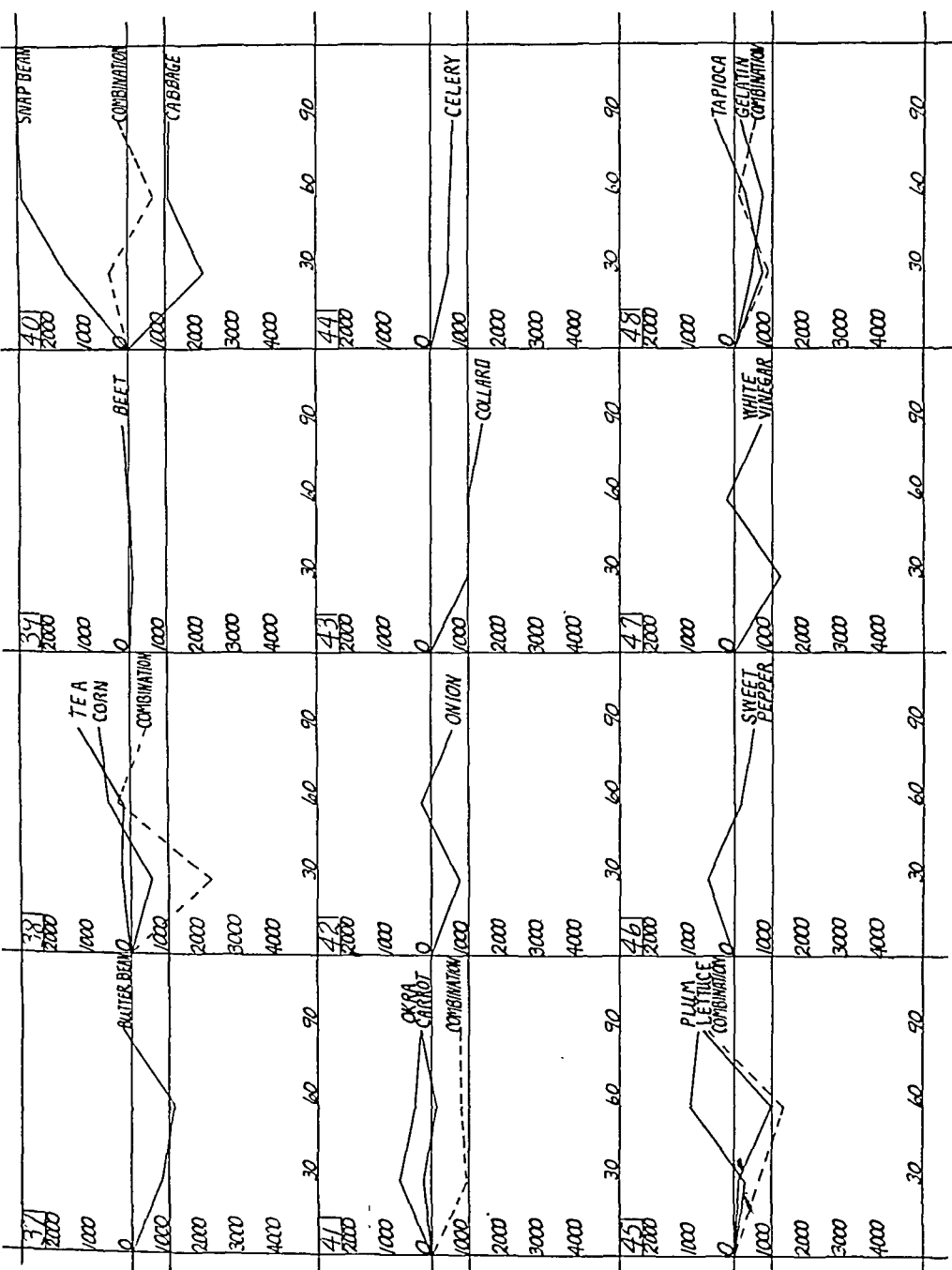


FIG. 4.—Curves of individual foods and combinations of foods (Graphs 37 to 48).

were run as quickly as possible after completing the individual tests, but each individual test and each combination test were run on a separate day.

TABLE 1.—FASTING AND POSTPRANDIAL LEUKOCYTE AND BODY TEMPERATURE RESPONSES TO SEPARATE FOODS.

No.	Date.	Food.	Fast- ing.	30.	60.	90.	Index.	Temperature.					Symptoms.
								Fast- ing.	30.	60.	90.	120.	
1	10-10-37	Pear	10425	8250	7550	7900	-2525	None
2	10-11-37	Steak	8950	7350	6700	7000	-1950	Mild heartburn
3	10-12-37	Rice	9850	6400	6200	7700	-3084	Diarrheal stool
4	10-13-37	Hominy grits	8750	7150	7850	8200	-1017	None
5	10-14-37	Sweet potato	10650	5850	6400	8400	-3767	Heartburn, belching, dizziness
6	10-15-37	Irish potato	7950	7100	6050	8650	-684	Heartburn, diarrheal stool
7	10-16-37	Sweet milk	8850	8450	8000	6500	-1200	None
8	10-22-37	Cane sugar	9550	8950	7250	7300	-1717	Drowsiness, dizziness
9	10-23-37	Salt	8200	7700	6200	6850	-1284	Diarrheal stool
10	10-25-37	Water	9450	6750	6350	7000	-2750	None
11	10-26-37	Black pepper	9800	8100	7850	7800	-1847	None
12	11-3-37	Egg	9300	9100	8250	8350	-734	Mild heartburn
13	12-9-37	Wheat	8150	7250	6700	6200	-1434	Mild heartburn
14	12-13-37	Salt Bacon	7600	9150	8400	6950	+566	Mild heartburn
15	12-15-37	Salt ham	6300	7700	7300	5950	+693	None
16	12-23-37	Cane sugar	6450	6050	6000	6050	-417	Mild heartburn
17	12-24-37	Coffee	6950	6250	6500	8650	+183	None
18	12-26-37	Egg	6500	7000	7150	8800	+1150	Mild heartburn
19	12-31-37	Tobacco	6900	7200	7650	7350	+500	Heartburn, dizziness
20	1-4-38	Ether	6150	6000	6150	5900	-134	Faintness, headache
21	1-6-38	Water	5800	6550	5650	6400	+400	None
22	1-7-38	Salt	5250	5550	5950	5600	+450	Desire for stool
23	1-8-38	Kid	6450	6200	6100	5750	-434	None
24	1-10-38	Alcohol	5700	5500	6100	5550	+16	Dizziness, grogginess
25	1-11-38	Orange	5350	5350	4850	6150	+100	Heartburn
26	1-12-38	Apple	6650	5000	5350	6850	-917	Belching, bowel unrest
27	1-13-38	Banana	6450	4350	4850	6350	-1267	None
28	1-15-38	Salmon	5100	4900	6400	7300	+1100	Belching, headache
29	1-18-38	Lemon	5750	6650	5150	5000	-150	Desire for stool, fatigue
30	1-19-38	Spinach	6350	6500	7400	6650	+500	Bowel unrest, fatigue
31	1-21-38	Grapefruit	5250	4900	6000	5500	+216	Bowel unrest, fatigue
32	1-26-38	Rye	6700	5600	5600	6150	-917	None
33	6-6-38	Peach	6300	5750	5000	5900	-750	Desire for stool
34	6-9-38	Pineapple	7100	5950	5550	6250	-1184	Sneezing, headache
35	6-23-38	Tomato	6800	6000	5950	6400	-684	Headache
36	6-24-38	Pea	6000	5150	6100	5200	-517	None
37	6-30-38	Watermelon	7050	6050	5650	7200	-750	None
38	7-1-38	Cantaloupe	6000	5600	5100	6150	-384	Drowsiness, headache
39	7-7-38	Squash	5650	4150	5600	5600	-534	None
40	7-8-38	Cucumber	5300	6050	4800	5450	+133	None
41	7-14-38	Fig	5400	4900	5750	6300	+250	None
42	7-15-38	Grape	8150	6550	7500	7500	-967	None
43	7-20-38	Tea	6350	6600	6550	7750	+616	None
44	7-21-38	Corn	5850	5300	6450	6700	+300	None
45	7-22-38	Butterbean	6500	5650	5350	6700	-600	Heartburn, belching, flatus
46	7-27-38	Beet	6050	6000	6050	6150	+16	None
47	7-28-38	Snap bean	7000	8650	9850	10000	+2500	98.70	99.00	98.80	98.95	98.60	None
48	7-29-38	Cabbage	6900	4850	5800	5800	-1417	98.58	99.80	98.80	98.90	98.50	Cramping, belching, diarrhea
49	8-3-38	Carrot	5650	5850	5500	5900	+100	98.60	98.70	98.80	98.81	98.76	Desire for stool
50	8-4-38	Okra	5950	6750	6350	6200	+483	98.60	98.79	98.60	98.59	98.59	None
51	8-5-38	Onion	6950	6200	7200	6350	-367	98.60	99.00	98.99	98.84	98.84	Drowsiness
52	8-8-38	Collard	7250	6250	6250	5900	-1117	98.47	98.81	98.80	98.80	98.80	None
53	8-9-38	Celery	6300	5800	5800	5700	-534	98.38	98.70	98.62	98.58	97.80	Epigastric pain
54	8-10-38	Lettuce	6450	6350	5450	7250	-100	98.65	98.78	98.76	98.70	98.40	Drowsiness
55	8-11-38	Plum	6200	5900	7300	7150	+583	98.60	98.76	98.60	98.60	98.58	None
56	8-13-38	Sweet pepper	11100	11750	10900	10600	-17	99.40	99.39	99.50	99.30	99.30	None
57	8-15-38	White vinegar	5750	4500	5850	5050	-617	98.65	98.93	98.80	98.95	98.60	None
58	8-16-38	Gelatin	6000	5500	5250	5850	-467	98.78	98.90	99.00	98.75	98.60	None
59	8-17-38	Tapioca	4900	4150	4600	5400	-184	98.58	98.57	98.50	98.60	98.78	None
60	8-18-38	Maple syrup	4750	4350	5050	4500	-117	98.45	98.78	98.70	98.90	98.20	Slight nausea
61	8-20-38	Honey	5900	5150	5750	5550	-417	98.50	98.62	98.70	98.60	98.40	Slight nausea
62	8-21-38	English pea	5550	5550	5350	5350	-134	None

TABLE 1.—FASTING AND POSTPRANDIAL LEUKOCYTE AND BODY TEMPERATURE RESPONSES TO SEPARATE FOODS.—*Continued.*

No.	Date.	Food.	Fast- ing.	30.	60.	90.	Index.	Temperature.					Symptoms.
								Fast- ing.	30.	60.	90.	120.	
63	8-23-38	Raw peanut	5750	5250	5800	5600	-200	98.58	98.68	98.60	98.60	98.10	None
64	8-26-38	Cocoa	5650	6300	5950	5600	+300	98.61	98.80	98.91	99.20	99.00	Desire for stool
65	8-27-38	Cinnamon	5850	5300	4750	4700	-934	98.42	98.58	98.60	98.61	97.70	None
66	8-29-38	Mustard	6800	6900	7100	7700	+433	98.58	98.60	98.70	98.78	98.62	Slight nausea
67	8-31-38	Chicken	5600	5750	4300	5250	-500	98.78	98.98	98.76	98.95	97.40	None
68	9-1-38	Asparagus	6550	6750	6450	6150	-100	98.75	98.83	98.70	98.70	98.65	None
69	12-7-38	Oyster	7700	6950	5750	7200	-1067	98.40	98.62	98.80	98.61	98.00	Heartburn, sour stomach
70	12-8-38	Trout	7400	5950	6700	8500	-350	98.20	98.63	98.70	98.80	98.90	Heartburn, belching
71	12-9-38	Shrimp	6500	6300	6200	6600	-134	98.30	98.90	98.95	98.80	98.75	None
72	12-14-38	Almond	5450	6700	5850	7100	+1100	98.25	98.65	98.75	98.60	98.60	None
73	12-15-38	Pecan	6800	6650	6500	6400	-284	98.10	98.60	98.50	98.55	98.55	None
74	12-16-38	English walnut	5750	6550	7150	7500	+1316	98.15	98.55	98.60	98.60	98.75	None
75	12-19-38	Fresh pork	4800	4850	6000	5500	+650	98.25	98.55	98.58	98.61	98.75	None
76	12-20-38	Yeast	5900	5250	5250	5200	-667	98.20	98.60	98.62	98.62	98.84	None
77	12-21-38	Coconut	6450	5750	5050	5900	-884	98.58	98.62	98.60	98.62	98.58	None
78	12-28-38	Clove	6900	5500	6350	6250	-867	98.30	98.60	98.65	98.58	98.56	None
79	12-29-38	Cranberry	6700	7400	6700	6850	+283	98.40	98.58	98.60	98.75	98.60	Diarrheal stool
80	1-1-39	Turkey	6000	5250	5450	6000	-434	98.25	98.50	98.50	98.80	98.42	None
81	1-3-39	Nutmeg	6350	5650	5800	5450	-717	98.00	98.60	98.63	98.68	98.58	None
82	1-4-39	Ginger	6950	6550	6500	5450	-784	98.25	98.60	98.72	98.80	98.58	None
83	1-12-39	Prune	8850	6850	5900	7100	-2234	98.10	98.58	98.61	98.65	98.68	Nausea, diarrheal stool
84	1-18-39	Cauliflower	5350	4750	6400	7150	+750	98.42	98.56	98.50	98.40	98.70	None
85	1-19-39	Turnip	6500	5650	5750	6450	-550	98.38	98.30	98.40	98.52	98.60	None
86	1-25-39	Eggplant	6550	6700	6700	6550	-200	98.20	98.58	98.41	98.56	98.60	None
87	2-2-39	Apricot	6250	5200	6450	5950	-384	98.57	98.50	98.61	98.61	98.50	Stool, abdominal cramps
88	2-3-39	Avocado	5350	6200	5900	6550	+866	98.60	98.84	98.89	98.90	98.65	None
89	2-10-39	Cod-liver oil	5000	5500	5850	4650	+333	98.50	98.56	98.70	98.70	98.59	None
90	2-11-39	Olive oil	6250	6200	5850	6100	-200	98.30	98.41	98.58	98.50	98.24	Slight nausea
91	2-16-39	Wesson oil	6750	5450	6900	6700	-400	98.58	98.61	98.58	98.56	98.50	None
92	2-17-39	Sesame oil	5100	5000	5200	5500	+133	98.50	98.61	98.74	98.58	98.59	Nausea, diarrhea
93	2-23-39	Beer	6250	5900	5300	5400	-717	98.05	98.60	98.72	98.73	98.58	Dizziness
94	2-26-39	Whiskey	5700	5150	6500	5550	+33	98.56	98.58	98.61	98.90	98.65	Dizziness
95	3-7-39	Rice	4850	6150	5450	6650	+1233	98.12	98.40	98.35	98.25	98.36	None
96	3-8-39	Irish potato	6200	5500	6350	5600	-384	98.04	98.43	98.47	98.50	98.46	Belching, sour stomach
97	3-9-39	Sweet potato	6400	5400	6150	6300	-450	98.23	98.40	98.56	98.40	98.41	Belching, sour stomach
98	3-11-39	Oatmeal	5050	5050	5800	6300	+666	98.40	98.62	98.58	98.59	98.60	None
99	3-15-39	Soybean	6350	6050	5450	7200	-617	98.40	98.60	98.60	98.64	98.56	Slight sour stomach
100	3-16-39	Barley	5050	6000	5000	5100	+316	98.62	98.78	98.83	98.69	98.48	None
101	3-19-39	Buckwheat	7000	6300	6950	7050	-234	98.42	98.62	98.68	98.60	98.58	None
102	4-15-39	Rhubarb	7400	7150	7050	7000	-334	98.40	98.40	98.59	98.39	98.20	None
103	4-18-39	Radish	6300	7700	6150	6800	+583	98.30	98.61	98.60	98.40	98.60	None
104	4-19-39	Pumpkin	7550	5400	6050	6550	-1553	98.30	98.59	98.61	98.67	98.40	Bowel unrest, rumbling
105	5-14-39	Dewberry	7400	6500	6350	6850	-834	98.50	98.61	98.57	98.61	98.52	None
106	5-15-39	Strawberry	6600	6350	6250	7850	+216	98.29	98.80	98.73	98.58	98.65	Stool
107	6-18-39	Cherry	6500	6500	6050	6650	-100	98.60	98.84	98.70	98.70	98.59	None
108	6-19-39	Blackberry	7050	5800	5800	8050	-500	98.62	98.50	98.65	98.80	98.65	None
109	6-20-39	Raspberry	6600	6200	7750	6350	+100	98.59	98.75	98.76	98.90	98.57	None
110	9-19-39	Sweet potato	8050	6100	7000	7850	-1067	98.60	98.65	98.68	98.60	98.50	Sour stomach, heartburn
111	9-20-39	Beef	7500	7050	7400	6550	-467	98.40	98.78	98.78	98.70	98.80	None
112	9-21-39	Pear	7050	7150	7850	8000	+616	98.40	98.59	98.56	98.58	98.40	None
113	9-25-39	Lamb	7450	8350	8300	7650	+716	98.65	98.80	98.90	99.20	99.00	None
114	9-26-39	Date	6650	6750	6450	7600	+283	98.80	98.79	98.75	98.62	98.60	Slight belching

In Table 1, data on the tests of the 101 foods are tabulated in chronologic order. The table lists 114 foods, actually, due to repeat tests on 10 foods. In addition, data are submitted on tobacco, ether and alcohol. For the tobacco test, a cigar was smoked, continuously, after the fasting count. For the ether test, inhalations of ether were used at intervals after the fasting count. In the alcohol test, 1 ounce of 95% alcohol was ingested, diluted with an equal quantity of water. Fasting and postprandial counts of each test are listed. Readings for body temperature, beginning with snap bean, the thirty-eighth food, are listed. Fasting and postprandial temperature readings, made immediately preceding each count and at 30 minutes after the final count, are recorded. Symptoms resulting from the ingestion of each food, are recorded also. Under the item, index, the author assigns a numerical value to the leukopenic index of each food. It is derived by obtaining the mean value of the 3 postprandial counts which is compared to the value of the fasting count. The variation above or below the fasting count is taken as the value of the respective index, which is expressed in plus and minus values.

TABLE 2.—FASTING AND POSTPRANDIAL LEUKOCYTE AND BODY TEMPERATURE RESPONSES TO COMBINATIONS OF FOODS.

No.	Date.	Food.	Fast- ing.	30.	60.	90.	Index.	Temperature.					Symptoms.
								Fast- ing.	30.	60.	90.	120.	
1	10-17-37	Irish potato, steak	7750	7400	9650	8250	+683	None
2	10-19-37	Sweet milk, Irish potato, hominy grits	7650	5750	5300	5600	-2100	None
3	10-20-37	Pear, sweet potato, rice	9550	6750	6050	6250	-3200	Nervousness
4	10-29-37	Group A All foods Graph 8	8900	6700	8050	6050	-1967	None
5	12-27-37	Group B All foods Graph 15	8700	6950	6300	6350	-2167	Slight belching, slight heartburn
6	12-28-37	Wheat, egg	6900	6450	7650	7100	+166	Mild heartburn
7	12-29-37	Coffee, salt bacon	7250	8250	7750	7250	+500	None
8	12-30-37	Egg, coffee	6000	6800	8250	7450	+1500	Slight headache, slight belching
9	1-14-38	Apple, banana	7000	7100	5900	6450	-517	Flatus, bowel unrest
10	1-20-38	Lemon, orange	6650	5250	5550	5850	-1100	Bowel unrest, dizziness, headache
11	1-22-38	Orange, lemon, grapefruit	5200	5800	6850	6250	+1100	Fatigue
12	6-10-38	Peach, pineapple	5250	5350	5100	5100	-67	None
13	6-25-38	Pea, tomato	6450	5800	5600	6650	-434	None
14	7-2-38	Watermelon, cantaloupe	7150	5850	6400	6600	-867	None
15	7-9-38	Cucumber, squash	7250	6550	6350	7050	-600	None
16	7-18-38	Fig, grape	6900	6000	6450	5500	-917	Fatigue, drowsiness
17	7-23-38	Tea, corn	7350	5200	7650	6900	-767	None
18	7-30-38	Snap bean, cabbage	5700	6200	5050	5950	+33	98.81	99.00	99.20	99.20	99.20	Mild abdominal cramps, slight belching
19	8-6-38	Carrot, okra	7450	6500	6700	6700	-817	98.80	98.20	98.84	98.70	98.81	None
20	8-12-38	Lettuce, plum	7650	7000	6300	8400	-417	98.80	98.98	98.98	98.86	99.00	None
21	8-19-38	Tapioea, gelatin	6550	5650	6400	5950	-550	98.62	98.75	98.94	98.70	98.75	None
22	8-25-38	English pea, raw peanut	6350	6550	6700	7100	+433	98.62	98.81	98.95	98.80	98.98	Moderate heartburn
23	8-30-38	Cinnamon, mustard	5850	5950	5400	5350	-284	98.65	98.84	99.00	99.00	98.88	Nervousness
24	9-2-38	Chicken, asparagus	5650	5450	6200	5850	+183	98.80	98.82	98.62	98.85	98.75	None
25	12-10-38	Oyster, trout	7450	6300	6950	6100	-1300	98.20	98.55	98.65	98.60	98.60	Slight belching
26	12-17-38	English walnut, almond	7300	6100	6850	6600	-784	98.18	98.60	98.40	98.60	98.60	None
27	12-27-38	Yeast, coconut	5300	5300	5700	4900	0	98.40	98.92	98.70	98.80	98.84	None
28	1-2-39	Turkey, cranberry	6450	6650	6150	6250	-100	98.40	98.75	99.00	98.78	99.00	None
29	1-5-39	Cloves, ginger	7400	5150	5750	6100	-1734	98.40	98.60	98.70	98.70	98.70	None
30	1-26-39	Cauliflower, turnip	6450	5400	6000	5100	-950	98.25	98.70	98.75	98.60	..	None
31	2-4-39	Apricot, avocado	6550	6800	5200	5950	-567	98.50	98.60	98.62	98.65	98.58	None
32	2-12-39	Cod-liver oil, olive oil	6350	5500	5650	5800	-700	98.18	98.30	98.59	98.59	98.60	None
33	2-22-39	Wesson oil, sesame oil	6150	5750	5550	6150	-334	98.40	98.61	98.70	98.82	98.60	None
34	2-27-39	Beer, whiskey	6700	6000	5750	5750	-867	98.30	98.58	98.60	98.70	98.60	Dizziness
35	3-10-39	Rice, sweet potato	5950	6050	6150	6450	+266	98.40	98.59	98.57	98.62	98.50	Slight sour stomach
36	3-21-39	Oatmeal, soy bean	6800	5850	6850	6350	-450	98.35	98.65	98.56	98.78	98.78	Slight sour stomach, slight belching
37	3-22-39	Buckwheat, barley	6600	6400	6900	6100	-134	98.40	98.70	98.61	98.60	98.40	Slight sour stomach, slight belching
38	4-21-39	Pumpkin, radish	6950	6700	7650	7450	+316	98.41	98.28	98.61	98.58	98.59	Slight belching
39	5-16-39	Dewberry, strawberry	7350	6800	5950	6150	-1050	98.40	98.59	98.70	98.60	98.41	Slight abdominal cramps
40	6-21-39	Blackberry, raspberry	5350	4600	5800	7300	+550	98.75	98.79	98.82	98.83	98.80	None
41	9-22-39	Sweet potato, pear	7950	6450	7050	7750	-867	98.57	98.60	98.60	98.59	98.50	Slight heartburn, slight belching, slight sour stomach
42	9-27-39	Lamb, date	6900	6150	7600	7300	+116	98.54	98.82	98.72	98.79	98.61	None

In Table 2, data on the tests of the 42 combinations of foods are tabulated in chronologic order. The data are arranged, similarly to those in Table 1. Beginning with the eighteenth combination, readings are given for body temperature.

In producing the graphs, indices were run on a group of foods at daily intervals. If two or more foods were found which produced

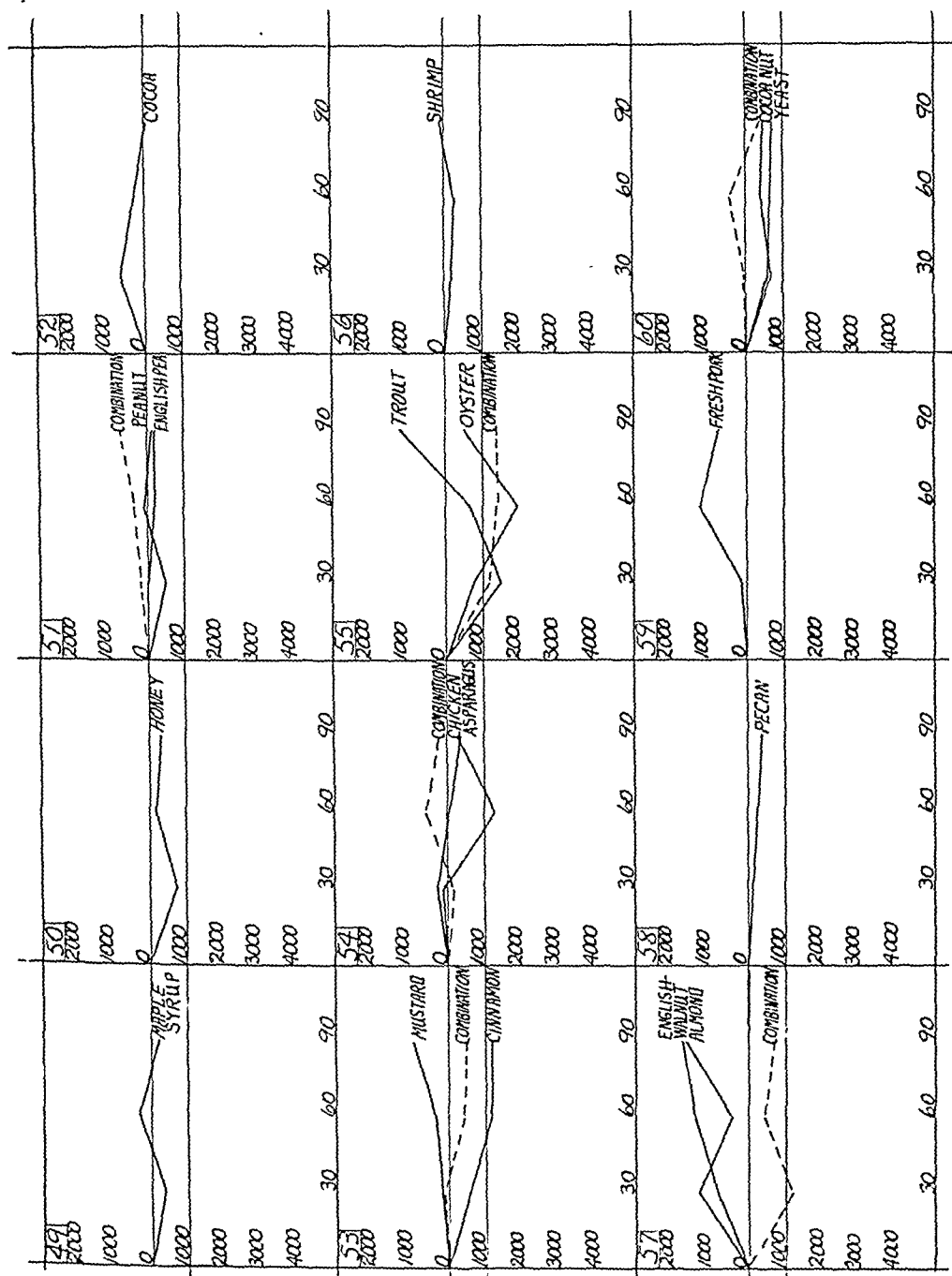


Fig. 5.—Curves of individual foods and combinations of foods (Graphs 49 to 60).

a leukocytosis when tested individually, they were chosen for a combination test in anticipation that the combination response

would be a leukocytosis. If two or more foods were found which produced a leukopenia when tested individually, they were chosen

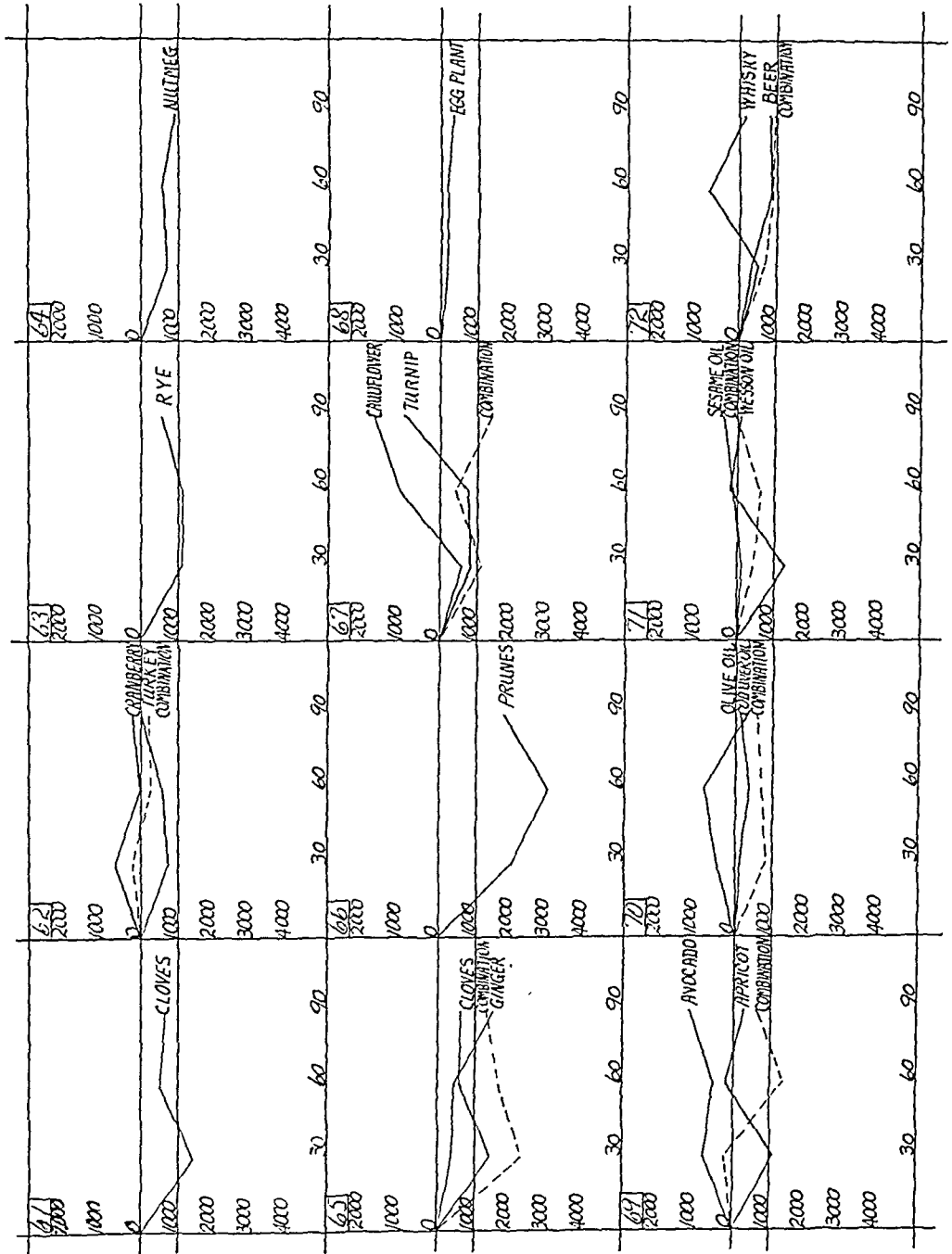


FIG. 6.—Curves of individual foods and combinations of foods (Graphs 61 to 72).

for a combination test in anticipation that the combination response would be a leukopenia. If two or more foods were found which did

not produce a leukocytosis or a leukopenia greater than 1000 cells when tested individually they were chosen for a combination test in

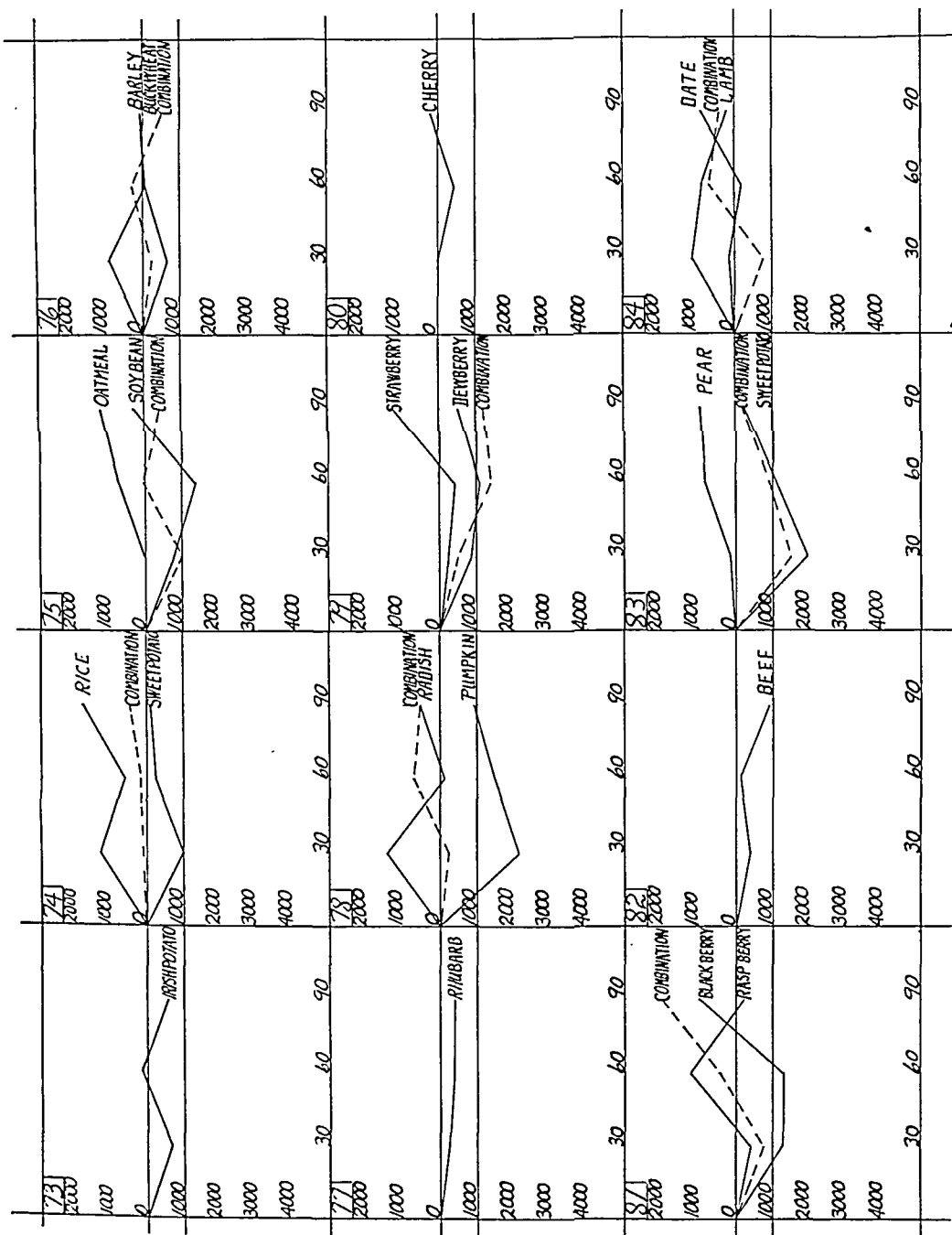


Fig. 7.—Curves of individual foods and combinations of foods (Graphs 73 to 84).

anticipation that the combination response would be a similar one. Finally, if one food was found that produced a leukocytosis and

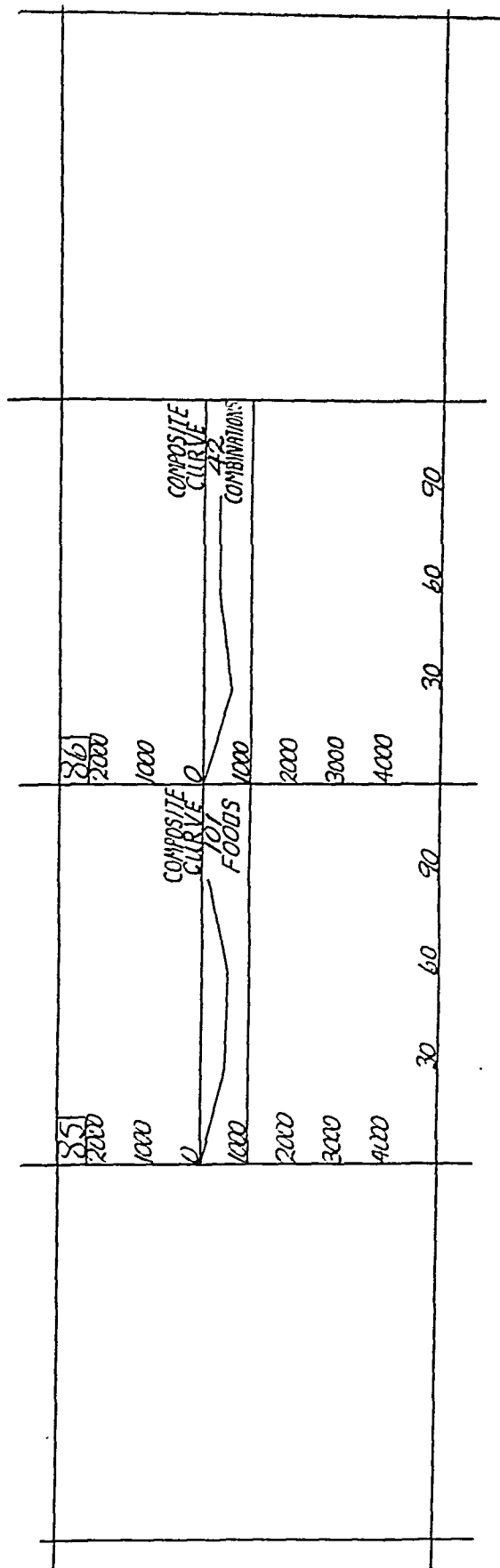


FIG. 8.—Composite curves of 101 foods and 42 food combinations (Graphs S5 and S6).

another was found that produced a leukopenia, a combination of two such foods was chosen in anticipation that the combination response would be a neutralizing or composite response of the individual leukocyte responses. Through such graphs the author felt that the 4 hypothetical questions which were asked on page 14 could be answered by depicting that the ingestion of food may influence the manner of response of the leukocytes to both single foods and to combination of foods.

In Graph 85 (Fig. 8) a composite curve is given of the curves of the 101 individual foods. It represents the mean of each of the 3 respective postprandial counts, as compared to the mean of the fasting counts, which is represented as being at the zero position of the ordinates.

In Graph 86 (Fig. 8) a composite curve is given likewise of the curves of the 42 combinations of foods.

Results and Comments. The first leukopenic index was performed on October 10, 1937 (Table 1). Indices were run then with foods, some of which the author felt disagreed distinctively with him, such as pear, steak (beef), rice, hominy grits, sweet potato, Irish potato, sweet milk and black pepper. Their curves and combination curves are seen in Graphs 1 to 8. They show the greatest variation in cells of any in the series. When the investigation was begun, the author had a high fasting count. This may have influenced the magnitude of the leukocyte response, as suggested by Balyeat.² In regard to symptoms, rice, sweet potato, and Irish potato definitely disagreed. Invariably sweet potato produced heartburn and sour stomach when eaten. Based upon the indices obtained, rice, sweet potato, pear, and milk were omitted from the diet. Milk was omitted for nearly 2 years. Rice, pear and sweet potato were omitted for a period of more than a year and were eaten again to make repeat tests (Graphs 73 to 84). Due to the omission of these foods, the author feels that he has experienced practically complete relief from his sinus condition and amelioration of symptoms of an irritable colon. Relief from constipation and from a recurrent anal fissure followed, also. With the subsequent omission of egg, which caused a toxic "bilious" feeling, the colonic disturbance has been improved further. Repeat tests on Irish potato, sweet potato, rice and pear (Graphs 73 to 84) show different types of curves than did these foods (Graphs 1 to 8), which were tested $1\frac{1}{2}$ years previously. The curve for Irish potato is an indeterminate curve. The curves for rice and pear represent a leukocytosis instead of a leukopenia. Two repeat tests for sweet potato show an indeterminate and a leukopenic curve. The author feels that the omission of these foods may have resulted in acquiring a tolerance for them again.

The investigation extended over a period of 2 years, thus obviating the effects of seasonal influences. The same type of anticipated response of the leukocytes to combinations of foods was produced

at the end of the study as was produced in the initial period. During the early part of the study, repeat tests made on such foods, as salt, water, sugar, and egg show that the type of response of the leukocytes varied in phase (Graphs 1 to 24). It is of interest to study the curves for bacon, ham, and fresh pork (Graphs 10, 11 and 59). This pork was produced on the author's farm. The hogs were fed the same type of food, which consisted of corn, peanuts, peas, nuts and velvet beans. The meat was cured with the use of salt and refrigeration. The tests for bacon and ham made on December 13 and 15, 1937, show curves which are practically identical. The curve for fresh pork tested on December 19, 1938, is similar somewhat to those for bacon and ham.

The responses of the leukocytes to tobacco, ether and alcohol (Graphs 20, 21, 25) resulted in indeterminate curves.

At times the author experienced considerable fatigue. When such became quite evident, the studies were discontinued until he became refreshed again. Fatigue was particularly marked while running the tests on apple, banana, orange, lemon, grapefruit, peach, and pineapple (Graphs 25 to 32).

In regard to symptoms, foods which did not cause symptoms seemed to lessen those caused by other foods, when a combination of such foods was tested.

That the counting of 16 sq. mm. of cells at each count may result in a high degree of accuracy, in performing the leukopenic index is seen by many of the curves for single foods. Such curves do not oscillate 500 cells up or down. Some of them are essentially straight lines.

The composite curves of the 101 foods and of the 42 combinations of foods (Graphs 85 and 86) are indeterminate curves. These two types of composite curves, as well as those depicting the leukocyte response to the 42 combinations of foods, are shown for the first time in literature as far as the author can determine.

An analysis of the curves of the 101 foods reveals that 18.1% lie above the plus 1000 position of the ordinates of their respective graphs at one or more points; 46.8% lie entirely between the plus 1000 and minus 1000 positions, at all points; and 35.1% lie below the minus 1000 position, at one or more points. It is thus seen that in the author's response to individual foods a distinct leukocytosis is produced by a comparatively small number. A distinct leukopenia is produced by a larger number. His predominant response is an indeterminate one, in which neither a leukocytosis nor a leukopenia of any considerable degree is produced.

An analysis of the curves of the 42 combinations of foods reveals that 83.3% agree in type with the curves produced by the separate foods composing each combination; 9.5% are doubtful; while 7.1% disagree in this type of response. In deriving these percentages, the author interprets the leukocyte responses in Graphs 1, 38, 57

as disagreeing, those in Graphs 15, 30, 54 and 67 as being doubtful, and those in all remaining graphs as agreeing in the nature of their responses.

In approximately 50% of the combination tests the results of the response of the leukocytes were determined at the end of each test. In the remaining 50% the results were determined at the end of the investigative study. The results of the response of the leukocytes to the individual foods were determined at the end of each test, to know what foods to select for the combination tests. As far as the author could determine, the same general agreement in the type of response of the leukocytes to the combinations of foods was obtained in both groups, thus eliminating any psychologic factor.

The author takes into consideration that the element of chance and unavoidable errors in technique may have played a part in producing the type of curves seen in the various graphs. He hopes such graphs may stimulate further investigation, in research of this nature.

Concerning his sensitizations, as determined by the cutaneous and intracutaneous tests, oatmeal, pineapple, squash, pear, peanuts, rice and apple caused slight skin reactions. With regard to pollens, elm gave a 1+ intracutaneous reaction in a 1 to 500 dilution. The artemisia group components gave a 1+ intracutaneous reaction in a 1 to 500 dilution, while the chenopodiacea group components gave a 4+ intracutaneous reaction in this same dilution. Desensitization therapy to the pollen groups has not been instituted at the present writing.

Concerning the effects of food ingestion upon body temperature, there was an increase almost universally, after eating both individual foods and combinations of foods. This increase was not greater than 0.1° in some tests, while in others the increase was as much as 0.5° or more. In a few tests, no increase occurred. The author attempted to correlate any possible rise or fall in temperature to an associated increase or decrease in the leukocytes. No definite evidence was found that this slight increase of temperature influenced in a characteristic manner the postprandial leukocyte response to either single foods or to combinations of foods. In those tests in which there was an elevation of temperature preceding the fasting count a slight increase usually occurred, as in those tests in which the fasting temperature was normal. In those tests in which the temperature increased, a normal reading was usually obtained at the end of a 2-hour period.

Summary. 1. Leukopenic indices were obtained on 101 foods and 42 combinations of foods. Curves are presented of the fasting and postprandial leukocyte response at 30-minute intervals. Observations were made upon body temperature and symptoms are recorded resulting from food ingestion.

2. The author feels that the leukopenic index was of diagnostic

value in the present study. The test as proposed today is time-consuming and its application practical to only a limited number of foods, perhaps those known to be major allergens generally. If the ingestion of food can influence definitely the character of the leukocyte response, perhaps simpler tests may be evolved, based upon some phase of hematologic response to digestion.

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FAMILIAL MICROCYTIC ANEMIA.

OBSERVATIONS ON 6 CASES OF A BLOOD DISORDER IN AN ITALIAN FAMILY.

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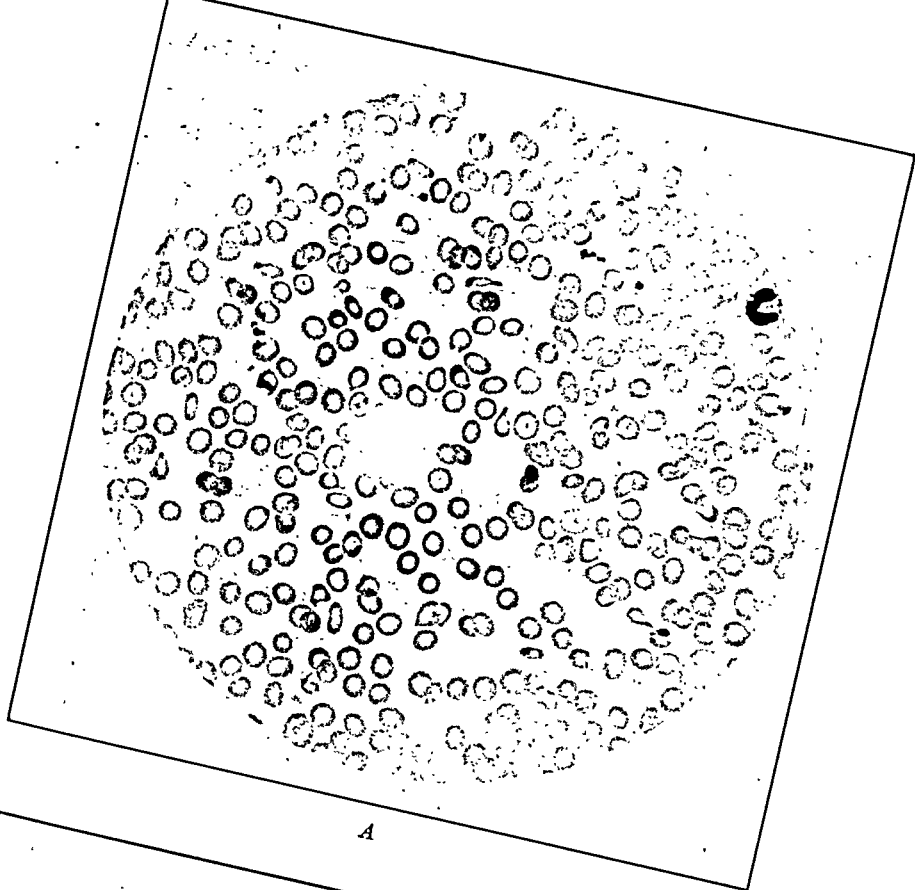
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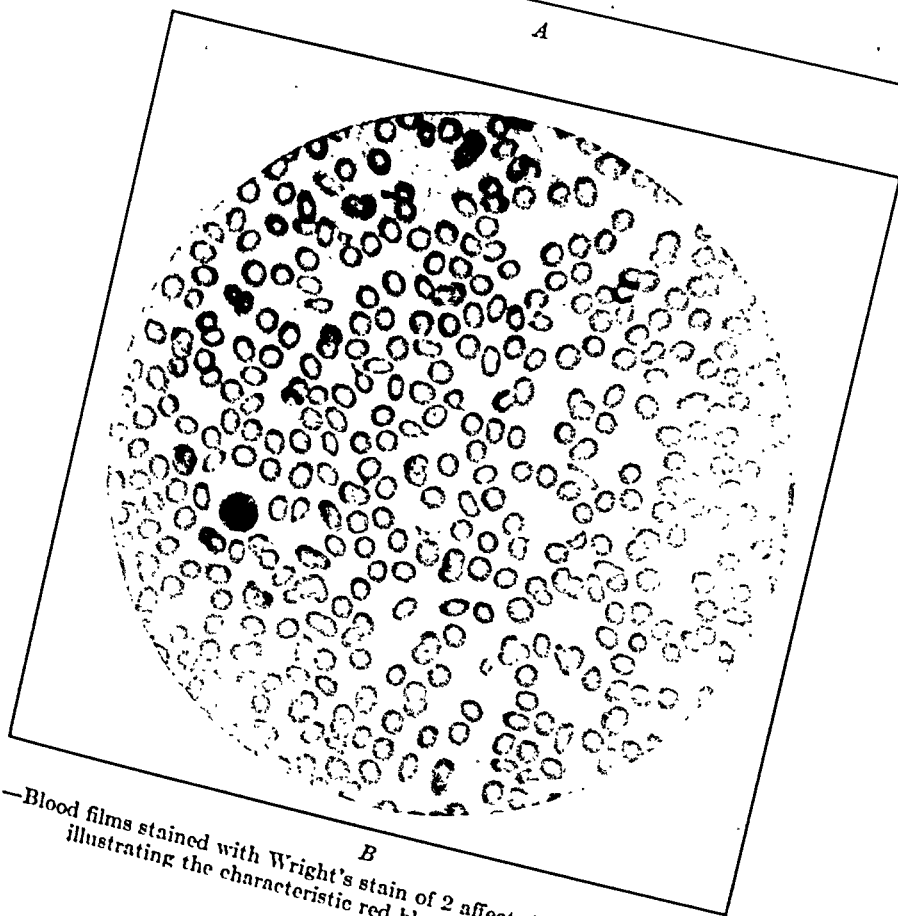
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FOLLOWING the chance discovery of an unusual blood picture in a woman of Italian descent first examined in 1934, studies were made of 20 other members of her family. Five of these were found to have a similar disorder and data obtained from hospital records indicated that 4 deceased members of the family had been anemic. As far as we have been able to determine, this condition has not hitherto been described. The results of the blood examinations of the 6 affected members of this family are shown in Table 1. It will



A



B

Fig. 1.—Blood films stained with Wright's stain of 2 affected members of the family illustrating the characteristic red blood cell morphology.

be noted that the erythrocytes number more than 5,000,000 per c.mm. in each case with a hemoglobin level of from 9.36 to 10.92 gm.



FIG. 2.—Roentgenogram of the skull of Mrs. L. D., aged 38, showing the granular appearance of the cortex. Similar changes have been observed in the other affected members of this family.

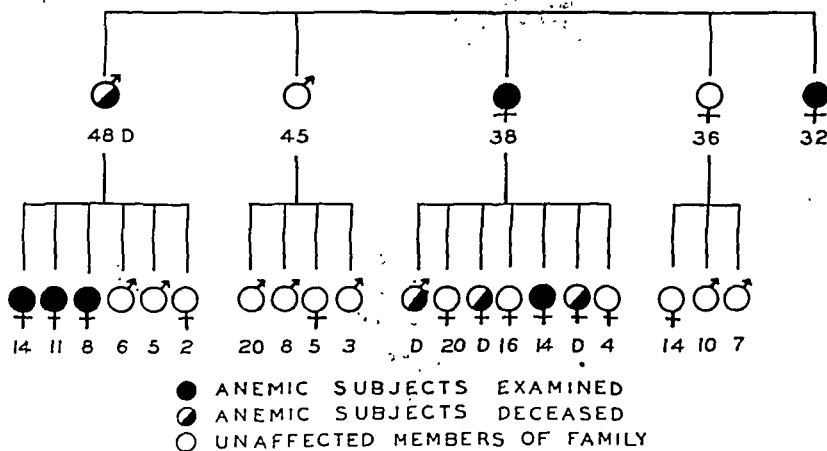


FIG. 3.—The inheritance of familial microcytic anemia. Numbers represent the ages of the individuals. D indicates deceased.

per 100 cc., a mean corpuscular volume of from 56.6 to 66.9 cubic micra, and hemolysis complete only in 0.15 saline solution. The icteric indices were normal, urobilinogen excretion in the urine

normal, leukocytes normal in number and differential percentage, platelets normal or increased. The variation in size and shape of the red blood cells is shown in photomicrographs of stained blood films of 2 affected individuals (Fig. 1). The granular appearance in Roentgen ray plates of the skull noted in each of the 6 individuals is illustrated in Figure 2. No other bony changes were observed.

The distribution of the 6 cases of this disorder among the 21 members of this family is shown in Figure 3. Also included are 4 deceased members who are known from hospital records to have suffered from an obscure type of anemia. None of these 4 individuals apparently died as a result of the anemia. The fact that affected members alone transmitted the disorder points to a Mendelian dominant type of inheritance.

TABLE 1.—BLOOD FINDINGS IN 6 CASES OF FAMILIAL MICROCYTIC ANEMIA.

Age	38	14	14	11	8	32
Sex	F.	F.	F.	F.	F.	F.
BLOOD EXAMINATION:						
Red blood cells, per c.mm.	5,130,000	5,620,000	5,200,000	5,330,000	5,830,000	5,200,000
Hemoglobin, %	60	70	65	64	64	68
Hemoglobin, gm. per 100 cc. blood	9.36	10.92	10.14	9.98	9.98	10.61
Hematocrit, %	32.0	37.6	33.2	32.1	32.9	32.8
Mean corpuscular volume, cubic micra	62.3	66.9	63.4	60.2	56.6	63.1
Mean corpuscular hemoglobin concentration, %	29.3	29.0	30.2	31.1	30.3	32.3
Mean corpuscular hemoglobin, micro-micrograms	18.2	19.4	19.5	18.7	17.1	20.4
Reticulocytes, %	3.1	3.2	1.2	1.2	1.6	0.7
Icteric index	5	5	4	5	4	5
Red cell resistance, % NaCl:						
Trace of hemolysis	0.42	0.42	0.46	0.42	0.42	0.40
Complete hemolysis	0.15	0.15	0.15	0.15	0.15	0.15
Platelets	+	++	++	N	++	++
White cells per c.mm.	6,700	7,700	7,800	6,700	6,800	9,100
Polymorphonuclear neutrophils, %	60.0	50.0	55.0	49.5	78.5	57.5
Polymorphonuclear eosinophils, %	4.0	7.5	1.5	2.0	1.0	5.0
Polymorphonuclear basophils, %	0.5	1.0	1.0	0.0	0.5	0.5
Small lymphocytes, %	12.5	17.5	19.5	17.0	7.0	18.0
Large lymphocytes, %	15.5	14.5	12.5	20.5	7.5	10.0
Monocytes, %	7.5	9.5	10.5	11.0	5.5	9.0
	100.0	100.0	100.0	100.0	100.0	100.0

+ signifies platelets present in increased numbers.

Therapy over periods of weeks to months with iron in full therapeutic doses by mouth (ferric ammonium citrate 6 gm. daily, ferrous sulphate 2 gm. daily) and by injection (green iron and ammonium citrates 100 mg. daily), with added copper (copper sulphate 20 mg. daily), with liver extract by injection (100 units daily), with raw liver (300 gm. daily) by mouth, with thyroid (2 gr. daily) and with high vitamin régimes was uniformly ineffective in altering the blood picture.

The only symptoms suffered by any of the 6 individuals with this disorder were those consistent with the relatively mild anemia present. Physical examinations were essentially normal. In no instance was splenomegaly present.

Discussion. The disorder of blood formation described above resembles both simple hypochromic anemia and, to a lesser extent, erythroblastic anemia (Cooley). Although multiple cases of these

conditions are not uncommon in families, there appears to be no specific type of inheritance involved in simple hypochromic anemia and erythroblastic anemia is transmitted as a Mendelian recessive.¹ In the absence of complications, simple hypochromic anemia responds to iron therapy. In general, at hemoglobin levels such as those observed in our 6 cases, there is less marked variation in red cell size and shape in simple hypochromic anemia. Increased resistance to hemolysis by hypotonic salt solution is common in simple hypochromic anemia and erythroblastic anemia as well as in the condition observed by us. In simple hypochromic anemia bone changes have not been noted, whereas in erythroblastic anemia they are commonly found not only in the skull but in many other parts of the skeleton. Erythroblastic anemia is further characterized by splenomegaly, erythroblasts in the peripheral blood, an elevated level of reticulocytes, an increased icteric index and other evidences of increased blood destruction.

Wintrobe² has recently presented a group of cases of peculiar anemia occurring in Italians, some of which may be identical with our cases, others of which are definitely dissimilar.

Summary. Six members of an Italian family, 21 of whom have been examined, have exhibited an unusual blood disorder. This condition is characterized by the following features:

1. Normal erythrocyte count, with marked variation in size and shape of the cells, marked microcytosis, moderate hypochromia, and increased resistance to lysis by hypotonic salt solution.
2. Moderate reduction in hemoglobin level (9 to 11 gm. per 100 cc. of blood).
3. Granular appearance of the skull in Roentgen ray plates.
4. Mendelian dominant type of inheritance of the syndrome.
5. Refractoriness of the anemia to all forms of therapy which have been attempted.

We are indebted to Miss Harriet MacDonald for technical assistance.

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THE DETERMINATIVE BACKGROUND OF SUBACUTE BACTERIAL ENDOCARDITIS.*

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If in any disease development takes place with frequency on a certain background of preëxisting conditions, and if this background

* This study was aided by a grant from the Milton Fund of Harvard University to study the accumulated clinical records of the Medical Service of the Peter Bent Brigham Hospital in Boston.

is recognized, the probability of the existence of the disease in question is enhanced very greatly. Such can be spoken of as the determinative background of a disease.

In this sense what is the determinative background on which the symptoms and signs of subacute bacterial endocarditis and more particularly, subacute *Streptococcus viridans* endocarditis develop? Strikingly in adults, to which this study of patients admitted to the Peter Bent Brigham Hospital is limited, an outstanding feature of the background has been rheumatic heart disease. To a very much less degree of frequency, probably because children below 12 years are not admitted to this hospital, has congenital heart disease served as a background.

If we consider as having rheumatic heart disease those patients with a definite past history of rheumatic fever or chorea and especially those with physical signs of cardiac enlargement or of valvular heart lesion in addition to a past history of rheumatic fever or chorea and those patients having no past history of rheumatic fever or chorea but with the physical signs of mitral stenosis or with the physical signs of aortic stenosis or of aortic insufficiency, the latter with a negative serum reaction for syphilis, we find that, of 150 consecutive adult cases of subacute *Streptococcus viridans* endocarditis, admitted between March 31, 1913 and September 1, 1939, 134 (89.33%) had rheumatic heart disease.

In this group of 150 patients with subacute *Streptococcus viridans* endocarditis it is noteworthy that only 1 patient had uncomplicated syphilitic aortic disease, while 3 other patients with syphilitic aortic disease had in addition rheumatic lesions as follows: 2 had rheumatic aortic stenosis with vegetations on the aortic cusps, normal mitral valves and syphilitic aortitis and 1 had rheumatic mitral stenosis with vegetations on the mitral valves and syphilitic aortitis and aortic insufficiency. The 1 patient with no rheumatic lesions showed syphilitic aortic disease with bacterial vegetations on the aortic cusps. Even in the presence of syphilitic aortic lesions, in only 1 patient did the bacterial lesions develop on a syphilitic valve lesion. This is further evidence of the predilection of the *Streptococcus viridans* to form vegetations on valves with rheumatic valvulitis.

In this series of adults there were 8 patients diagnosed as having a heart with congenital defect, 5 with either patent ductus arteriosus or interventricular septum defect (clinical diagnoses, no autopsy confirmation) and 3 with congenital anomaly of the aortic cusps (autopsy finding); of the latter cases 2 showed evidence of rheumatic heart disease. This seems a small number of patients with congenital heart defect, but it represents a large proportion of patients admitted to the Peter Bent Brigham Hospital with the clinical diagnosis of congenital heart disease. There were 36 of these, and as only 5 of the 8 here reported as having subacute bacterial endocarditis could have been diagnosed during life, this

group of 5 constitutes 13.88% of this hospital's clinical group of congenital heart disease. This is a higher percentage than that of the rheumatic heart disease group which developed subacute bacterial endocarditis of all forms. There were 157 of these, or 7.08%, of the 2,217 patients with clinical diagnosis of rheumatic heart disease admitted to the Peter Bent Brigham Hospital.

Among 150 adults with *Streptococcus viridans* endocarditis there were 8 patients who had no signs justifying a diagnosis of valvular heart disease and no past history of rheumatic fever or chorea; presumably these were non-rheumatic. Clinical study of 4 of these indicated that the heart was little, if any, enlarged and without physical signs of organic valve lesion; 3 more at autopsy showed the heart within normal limits of size and with normal valves; in 1, autopsy showed no organic valve lesions but moderately hypertrophied heart (440 gm. in weight). The last case would be grouped as a case of chronic non-valvular or chronic myocardial cardiac disease in the terminology used at this hospital.

It is a very striking fact that of 150 consecutive adult patients with subacute *Streptococcus viridans* endocarditis only 1 was demonstrated to have developed in a heart which was hypertrophied and free from organic valve lesions, when one considers that this latter is the preponderating type of chronic heart disease in the clinical diagnoses of patients admitted to this hospital, namely in 4,897 (65.4%) of 7,482 patients admitted in the same period of time with diagnosis of some form of chronic heart disease. The contrast between patients with subacute *Streptococcus viridans* endocarditis and those with chronic heart disease without bacterial endocarditis is shown in Table 1.

TABLE 1.—HEART DISEASE AT PETER BENT BRIGHAM HOSPITAL, MARCH 31, 1913 TO AUGUST 31, 1939.

Diagnostic grouping	150 patients with subacute strepto- coccus viridans endocarditis		7482 patients with chronic cardiac disease	
	No.	%	No.	%
Rheumatic*	134	89.33	2217	29.63
Congenital†	8	5.33	36	0.48
Congenital without rheumatic lesions	6	4.00		
Syphilitic‡	4	2.66	332	4.43
Syphilitic without rheumatic lesions	1	0.66		
Non-valvular	1	0.66	4897	65.45
Normal	7	4.66		

* Under rheumatic are included 5 cases with rheumatic lesions complicating other cardiac lesions, 2 with congenital and 3 with syphilitic lesions.

† Two of these hearts with congenital lesion showed in addition rheumatic lesions.

‡ Three of these hearts with syphilitic lesions showed in addition rheumatic lesions.

In addition to the 150 patients just discussed, in whom *Streptococcus viridans* was found, there were 7 patients with very similar clinical picture from whom other bacteria were isolated, 4 with *Staphylococcus albus*, 2 with unidentified staphylococci and 1 with a

pleomorphic bacillus a total of 7 cases of subacute bacterial endocarditis. In 6 of these the background was, by the criteria already stated, rheumatic heart disease, while 1 developed in congenital sub-aortic stenosis.

There were 17 patients in this study in whom the history, physical findings, fever curve and progression of disease were completely analogous to the patients in the series of 150 diagnosed subacute *Streptococcus viridans* endocarditis, but in whom cultural methods failed to demonstrate bacteria. All of these had 1 to numerous negative blood cultures during life; in 4 of them at postmortem examination bacteria were not demonstrated definitely in vegetations which in appearance suggested bacterial endocarditis. However, with so typical a clinical picture it seems justified to diagnose these as cases of subacute vegetative, probably bacterial, endocarditis. With the criteria of rheumatic heart disease as already given, in all of these 17 patients development of endocarditic disease had been on the background of rheumatic heart disease.

If these 17 are added to the 150 in which *Streptococcus viridans* was demonstrated and regarded as cases of subacute bacterial endocarditis in a bacteria-free stage when studied, and if the 7 cases with other bacteria causing subacute bacterial endocarditis, given in a preceding paragraph, are added, then we have had a total of 174 cases of subacute bacterial endocarditis, in which 157 (90.24%) had the background of rheumatic heart disease.

The absence of auricular fibrillation, too, is a definite feature of the background of subacute bacterial endocarditis. In the 150 cases of subacute *Streptococcus viridans* endocarditis only 4 (2.66%) patients were observed to develop auricular fibrillation. Of these, 3 had persisting auricular fibrillation, all with mitral stenosis and aortic insufficiency of long duration, 2 of which at autopsy showed hearts weighing 540 and 670 gm., while 1 with a history of rheumatic fever 31 years before had transient auricular fibrillation in the last few weeks of life. Another patient, in whom no bacteria could be demonstrated, had transient auricular fibrillation near the end of life, demonstrated only by feeling the pulse; this patient had had chorea 11 years before, and autopsy showed mitral stenosis in a heart weighing 320 gm. From these cases it would seem that auricular fibrillation develops in patients with subacute bacterial endocarditis very exceptionally (in 2.87% of all the cases); when it occurs it is, as a rule, in those with rheumatic heart disease long antedating the first evidences of bacterial endocarditis, who already have had some symptoms of congestive heart failure prior to the development of bacterial endocarditis.

Absence of prior cardiac decompensation of more than slight degree also is quite characteristic of the background of subacute bacterial endocarditis. Of our 150 patients with *Streptococcus viridans* endocarditis only 22 (14.66%) had noted shortness of breath before

onset of symptoms of the endocarditis, and 10 (6.66%) of these had experienced congestive heart failure of degree sufficient to constitute considerable handicap to their activities; only an occasional patient had suffered prior congestive failure to a degree

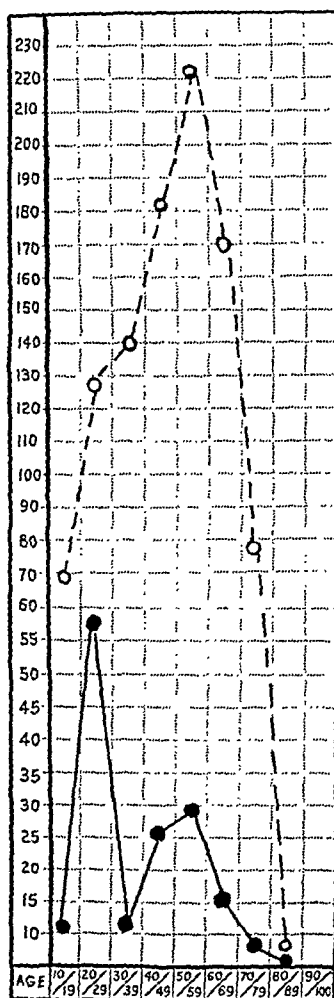


CHART 1.—Solid line shows number of patients with subacute *Streptococcus viridans* endocarditis in each ten year period from age 10 to 90. Broken line shows number of admissions to Medical Service of Peter Bent Brigham Hospital in the same age periods. Figures at bottom of chart show age in 10 year periods; figures at left of chart show number of patients.

needing prolonged bed rest. It would seem that, after marked congestive failure develops in the patient with rheumatic heart disease, there is little probability of the appearance of subacute bacterial endocarditis. For some unknown reason heart valves, which show chronic valvulitis or scarring, seem not very vulnerable to the *Strep-*

Staphylococcus aureus and other bacteria of similar pathogenicity after the more advanced clinical stages of chronic heart disease have been reached.

The valve vulnerability to *Streptococcus viridans* and other bacteria of low degree of virulence, as described in this paper, does not seem to apply in the case of acute non-rheumatic endocarditis, caused as a rule by bacteria of greater virulence, such as *Streptococcus hemolyticus*, *Staphylococcus aureus*, pneumococcus, and sometimes gonococcus, and usually part of a septicemia or occurring in an acute infectious disease such as pneumonia. At least in the autopsy records of this hospital, where 148 cases of acute non-rheumatic endocarditis were found, one-half (74) occurred in hearts with rheumatic valve disease and one-half (74) in heart with normal valves (contrast these figures with those in Table 1). Of the latter group (74 hearts) with normal valves, 21 hearts (28.37%) weighed 400 gm. or over, *i. e.*, were considerably to markedly hypertrophied, and 12 weighed between 350 and 399 gm., *i. e.*, were slightly hypertrophied. Those weighing 400 gm. or more without organic valve lesion would be grouped at this hospital as cases of chronic non-valvular or myocardial disease. In contrast to the 28.37% with acute endocarditis, subacute *Streptococcus viridans* endocarditis developed in only 1 heart of this type among 150 consecutive patients with subacute *Streptococcus viridans* endocarditis, or 0.06%.

Age seems to show a slight determinative background influence. Subacute *Streptococcus viridans* endocarditis occurred most frequently in the consecutive 150 adult cases in the age group 20-29 years (see Chart 1), as might have been expected from the known high incidence of rheumatic heart disease in youths and young adults. The age incidence of admissions to the Peter Bent Brigham Hospital (see Chart 1) was determined for 1,000 admissions, sampled by taking 100 consecutive admissions in each year of a 10-year period, and in order to reduce to a minimum any seasonal influence, selecting in each year the 100 patients from 2 months in successive rotation, so that all seasons of the year were proportionately represented. In contrast to the highest incidence of subacute *Streptococcus viridans* endocarditis cases being in the 20-29 year period, the highest incidence of admissions to this hospital fell in 50-59 year period. Chart 1 shows, however, that subacute bacterial endocarditis cases occur in all age periods and are not proportionately infrequent in the older groups, a fact that seems not to have been recognized very generally.

Sex shows a preponderance of males, 92 (61.33%) against 58 females (38.66%) in the 150 cases.

Summary. 1. If in any disease development takes place with frequency on a certain background of preëxisting conditions, and if this background is recognized, the probability of the existence of the disease in question is enhanced very greatly. Such can be spoken of as the determinative background of a disease.

2. The determinative background of subacute bacterial endocarditis is: (a) rheumatic heart disease, present in 89.33% of 150 consecutive adult cases of subacute bacterial endocarditis caused by the *Streptococcus viridans*, and in 90.24% of 174 consecutive adult cases of subacute bacterial endocarditis of all causes studied at the Peter Bent Brigham Hospital; (b) absence of auricular fibrillation, present in 2.66% of the *Streptococcus viridans* cases and in 2.87% of cases of all causes; (c) absence of prior cardiac decompensation, present in fairly marked degree in only 6.66% of the 150 cases and in severe form in only an occasional case; (d) youth and young adults (see Chart 1) and male sex (61.33% of the 150 cases).

THE EFFECTS OF TOBACCO SMOKE AND NICOTINE ON THE NORMAL HEART AND IN THE PRESENCE OF MYOCARDIAL DAMAGE PRODUCED BY CORONARY LIGATION.

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WHILE the possible injurious effects of tobacco and nicotine on the cardiovascular system have been widely investigated, there is as yet no unanimity of opinion regarding them. Attempts to produce arteriosclerosis in the experimental animal with nicotine also have met with equivocal results. In earlier experimental studies, it was concluded that arteriosclerotic changes resulted from nicotine,^{2,11} but after well-controlled studies, Thienes and Butt¹⁷ came to the opposite conclusion.

Since man only is commonly exposed to nicotine, most of the evidence bearing upon the harmful effects of nicotine has consisted of observations in humans. Some investigators believe that smoking may be harmful to the myocardium,^{6,13,16} while others feel that there is little proof for this contention.^{17,19}

Changes in the electrocardiogram in man following smoking have not infrequently been reported. Graybiel, Starr and White⁷ observed significant changes in 20 out of 45 subjects during smoking. Wilson²⁰ recently demonstrated that smoking produced *RT* deviations in patients with angina which, he suggested, might be the result of coronary spasm.

These findings led us to investigate the electrocardiographic effects of nicotine and tobacco smoke on the hearts of normal dogs and then upon the same dogs after the production of myocardial infarction by ligation of the anterior descending branch of the left coronary artery.

The Contents of Tobacco Smoke. The main constituents of tobacco smoke are nicotine, carbon monoxide and pyridine bases,⁵ of which nicotine is the most important.^{12,18} The effects produced by a solution of tobacco smoke in water are identical with those of nicotine. Carbon monoxide⁸ is seldom important in producing toxic effects from smoking; the amount absorbed is negligible since the smoke is freely diluted with air.¹ It has been shown¹ that a person in a room containing a large amount of tobacco smoke but not smoking himself may attain a carbon monoxide concentration in the blood as high as 5%.⁸ Concentrations in the blood as high as 8% have however been found after smoking, but even this figure is below the toxic level. It is possible however that toxic effects may ensue in some cases of pulmonary or cardiac disease when a mild grade of anoxia already exists.

Method of Study. The effects of nicotine on the heart were produced in the unanesthetized dog in two ways: 1, by the injection of nicotine in doses of 0.2 to 1.2 mg./kilo in a concentration of 2 mg./cc. in normal saline; 2, by the inhalation of tobacco smoke, accomplished by enclosing the dog's head in a box on one side of which was a celluloid window. Adequate aëration was permitted by the presence of numerous openings in this container. Tobacco smoke was blown into this box by means of positive pressure. The dog could thus be exposed to considerable amounts of nicotine by this method, though the amount inhaled obviously could not be measured.

In a number of instances, the effect in each unoperated dog was determined electrocardiographically several times. After control studies were complete, myocardial infarction was induced by exposing the heart and ligating the anterior descending coronary artery and its accompanying vein.³ Twenty-four hours after operation, the effects of nicotine or tobacco smoke were again determined and frequently thereafter during the acute and subacute stages of infarction. The effects in the chronic stage were determined for as long a period as 10 months following operation, though no data are recorded here beyond 45 days. In addition to the electrocardiographic observations, effects on respiration, blood pressure and the gastro-intestinal tract were noted. Necropsy studies were made at various stages of infarction.

Pathologic Changes Following Ligation of the Coronary Arteries. Ligation of a coronary artery sets off a series of events in the muscle involved, lasting for a variable period of time. First there are inaugurated the processes which lead to definite necrosis and which do not reach their maximum development for several days after the occlusion. These are followed by the slower process of healing. At the various stages in this somewhat protracted process, the histologic condition of the heart muscle varies greatly.

In an early stage, for a few minutes to $\frac{1}{2}$ hour after ligation, in spite of the presence of currents of injury as revealed by the electro-

cardiogram, little histologic evidence of infarction is present. Between this stage and that of maximum necrosis, the changes undergone by the muscle are great and more or less progressive. Just when the stage of maximum necrosis is reached is not always ascertainable. In the dog, usually 24 to 48 hours are required for its full development.

In the acute stage, 1 to 4 days after infarction, the muscle shows evidence of congestion, edema, hemorrhage and necrosis. At about 5 days, congestion and edema are no longer prominent, a line of demarcation is noted between the necrotic and living muscle which is emphasized by a well-defined zone of fibroblasts. At about 14 days, the size of the infarct has decreased considerably. At about 18 days, the site of infarction is a well-defined scar.⁹

Since the tolerance to nicotine might be related to and depend upon the pathologic changes in the involved muscle, we made frequent electrocardiographic observations (in addition to the normal control) in three stages: 1, the acute stage (approximately 1 to 4 days after ligation); 2, subacute stage (about 5 to 11 days), and 3, in the chronic stage (18 days to 10 months after the vascular occlusion).

Results. *General Effects of Nicotine and the Inhalation of Tobacco Smoke.* Following the inhalation of tobacco smoke, the respirations soon became rapid and deep. This was accompanied by an increase in blood pressure of from 50 to 100 mm. which lasted for 1 to 3 minutes.* During this time, an initial bradycardia was followed by acceleration of the heart beat and frequently the appearance of arrhythmias. Electrocardiograms were taken frequently during the period of change until they returned to normal. This usually occurred about 6 to 10 minutes after the inhalation was started. Nausea, vomiting and diarrhea occurred frequently towards the end of this period.

Following the intramuscular injection of nicotine, results identical to those that were recorded after smoke inhalation were observed. These occurred about $\frac{1}{2}$ to 1 minute following the intramuscular injection and were of the same character as those observed following the inhalation of tobacco smoke. The intensity of the reaction usually varied with the dose administered. Nausea, vomiting and diarrhea frequently occurred as an end reaction. This sequence of events usually lasted 3 to 8 minutes.

Severity of Nicotine Effects: Electrocardiographic Criteria. The effects of the intramuscular injection of nicotine on the electrocardiogram were determined in normal animals with doses of 0.2 to 1.2 mg./kilo. The alterations observed varied with the size of the dose and were graded as slight, moderate and marked.

While these changes merged one into the other, their demarcation

* Blood pressure records were obtained by means of the Hamilton manometer with the animal under light Nembutal anesthesia.

was fairly clear-cut and the severity of the alterations observed could be graded easily in this manner (Fig. 1). The same type of change was observed in different animals upon the same dose with a fair degree of consistency.

The following electrocardiographic changes were classified as slight: alteration in the direction of the *T* wave, sino-auricular heart block, sinus bradycardia, ventricular escape, simple tachycardia and occasional ventricular extrasystoles. These slight effects are not infrequently observed in the human subject after smoking 1 to 2 cigarettes. Moderate changes observed at a more advanced stage of the intoxication consisted of *RT* deviations, numerous extrasystoles, coupled rhythm and *A-V* dissociation with a fairly rapid ventricular rate. Marked electrocardiographic changes were observed at a still later period of intoxication and showed nodal tachycardia or ventricular tachycardia at a rate of 220 to 300 per minute. These tachycardias lasted from 1 to 42 minutes.

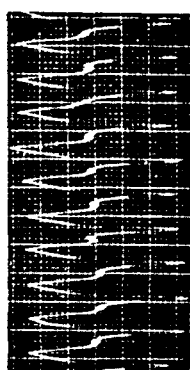
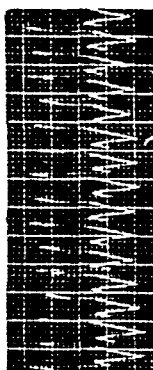
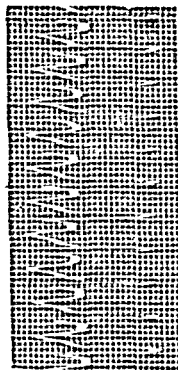
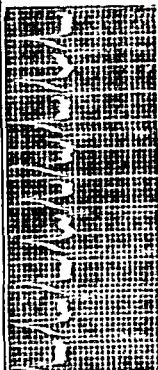
Comparison of Effects of Nicotine Intramuscularly With Inhalation of Tobacco Smoke. A considerable amount of nicotine can be absorbed by the animal from the tobacco smoke administered by the method already described. The inhalation of smoke from $\frac{1}{2}$ to $\frac{2}{3}$ of a cigarette often produced effects that were graded as marked. However, the effects were variable in different experiments due to variation in depth of respiration and consequently the degree of absorption of nicotine. In the dogs in which myocardial infarction was induced, the effects of tobacco smoke on the whole were much more marked than in the undamaged heart. Considerable differences in effects were also observed in this group.

In agreement with other workers, we have observed that the inhalation of tobacco smoke yielded qualitatively similar effects on the respiration, blood pressure and gastro-intestinal tract as those produced by the injection of nicotine. The electrocardiographic changes were also found to be the same. In our later experiments we resorted to the intramuscular injection of nicotine because the amount absorbed could be very easily controlled. In this manner, alterations were obtained which were quite comparable in different experiments.

As a control, in some animals, we resorted to the inhalation of smoke from excelsior (wood shavings) for longer periods of time than were used in the inhalation of tobacco smoke. The electrocardiographic alterations were slight and the systemic effects observed following the inhalation of tobacco smoke were absent.

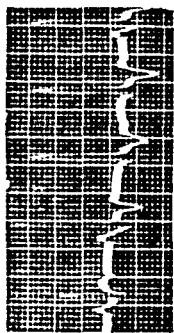
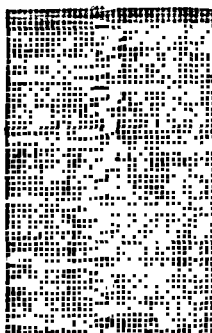
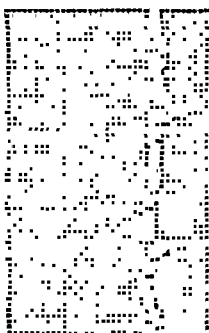
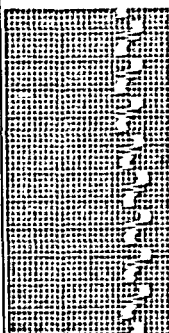
Effects of Nicotine on the Electrocardiogram of Normal Animals. (See Table 3.) Forty-one experiments were performed where the action of nicotine in normal animals was determined. In doses of from 0.2 to 0.6 mg./kilo, the effects were graded as slight. In experiments where 0.8 mg./kilo was used, marked effects were obtained in 2, moderate in 1 and slight effects in 8. Thus in 73% of

Marked



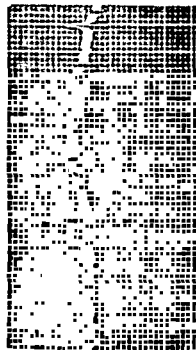
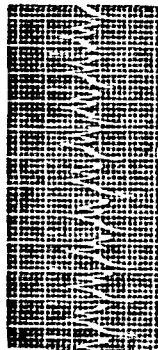
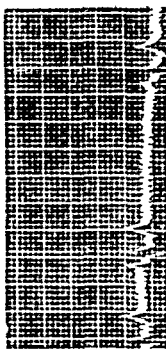
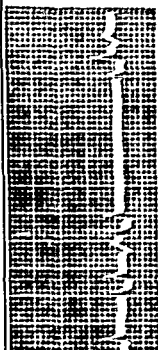
D

Moderate



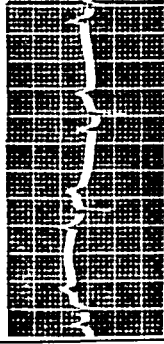
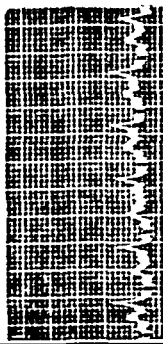
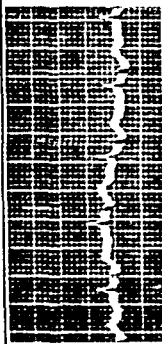
C

Slight



B

Normal



A

LI

LI

LI

LI

the experiments, a slight effect was obtained with this dose. In 2 experiments with 1 mg./kilo, slight effects were obtained; in 5 experiments with 1.2 mg./kilo, marked effects occurred in 4 and moderate in 1.

Effects of Nicotine in the Acute and Subacute Stage of Myocardial Infarction. Thirty-two experiments were performed in animals during the acute stage of myocardial infarction (1 to 4 days) following coronary artery ligation. As seen in Table 3 marked effects were obtained in most cases and moderate effects in the rest.

During the subacute stage (5 to 11 days), 25 experiments were performed. In the smaller doses, the effects were equally distributed between slight, moderate and marked. In the larger doses marked effects predominated (see Table 3).

Effects of Nicotine in the Chronic Stage of Myocardial Infarction. Thirty-nine experiments were performed during the chronic stage of myocardial infarction (18 days to 10 months). In a dose of 0.2 mg./kilo, slight effects were observed in 2 experiments. With 0.4 mg./kilo marked effects were observed in 2, moderate in 2 and slight in 8 (66%). With 0.6 mg./kilo, marked effects were observed in 3, moderate in 1 and slight in 5 (72%). In a dose of 0.8 mg./kilo, marked effects were observed in 5 (28%), moderate in 9 (50%) and slight in 4 (22%).

TABLE 1.—EFFECT OF NICOTINE ON THE ELECTROCARDIOGRAM OF A DOG BEFORE AND AFTER MYOCARDIAL INFARCTION. (DOG 597.)

Weight in kilograms.	Days following coronary ligation.	Dose per kilogram.			
		0.2 mg.	0.4 mg.	0.6 mg.	0.8 mg.
9	Before ligation	Slight	Slight	Slight	Slight
8.75	1	Marked			
"	2	Marked			
"	3	Moderate	Moderate		
"	4	Marked			
"	5	Slight	Moderate		
9	9	Marked		
"	19	Slight	Slight	Slight
"	20	Moderate
"	21	Slight

TABLE 2.—EFFECT OF NICOTINE ON THE ELECTROCARDIOGRAM OF A DOG BEFORE AND AFTER MYOCARDIAL INFARCTION. (DOG 321.)

Days following ligation.	Weight in kilograms.	Nicotine dose per kilogram.			
		0.2 mg.	0.4 mg.	0.6 mg.	0.8 mg.
Before	13.2	Slight	Slight	Slight	Slight
1	"	Marked			
2	"	Moderate	Marked		
3	"	Moderate	Marked		
4	"	Marked		
5	"	Moderate		
6	"	Marked		
8	"	Slight		
11	"	Marked	
33	12.3	Slight	Marked
45	12.0	Moderate
		Moderate

TABLE 3.—SUMMARY OF EXPERIMENTS SHOWING EFFECTS OF NICOTINE ON NORMAL DOGS AND DOGS WITH MYOCARDIAL INFARCTION.

	EKG effects.	Nicotine dose per kilogram.							
		0.2 mg.		0.4 mg.		0.6 mg.		0.8 mg.	
		No. exp.	Exp. in %.	No. exp.	Exp. in %.	No. exp.	Exp. in %.	No. exp.	Exp. in %.
NORMAL DOGS	Marked	0	0	0	0	0	0	2	18
	Moderate	0	0	0	0	0	0	1	9
	Slight	7	100	9	100	7	100	8	73
INFARCTED DOGS Acute (1-4 days)	Marked	13	68	11	84				
	Moderate	6	32	2	16				
	Slight	0	0	0	0				
Subacute (5-11 days)	Marked	2	33	4	33	4	66	1	100
	Moderate	2	33	3	25	1	17	0	0
	Slight	2	33	5	42	1	17	0	0
Chronic (over 18 days)	Marked	0	0	2	17	1	13	5	28
	Moderate	0	0	2	17	1	13	9	50
	Slight	2	100	8	66	5	72	4	22

Summary of the Electrocardiographic Effects. As will be seen from Tables 1, 2 and 3 and from Figure 2, normal animals have a considerable range of tolerance. Slight effects were observed in all experiments with a dose up to 0.6 mg./kilo, marked and moderate effects being observed only with doses of 0.8 mg./kilo and in only 27% of experiments with this dose; following coronary artery ligation in the acute stage of infarction, no slight effects were recorded in this stage. Marked effects were present in 68% and 84% and moderate in 32% and 16% with doses of 0.2 mg./kilo and 0.4 mg./kilo respectively. As the subacute stage is reached, larger doses of nicotine are required to produce marked and moderate effects. In other words, with healing of the infarcted area, larger doses are required to produce electrocardiographic changes similar to that produced by smaller doses in the acute stage. In the subacute stage, marked effects were observed in one-third of the cases with 0.2 mg./kilo, one-third with 0.4 mg./kilo and two-thirds with 0.6 mg./kilo. In the chronic stage, the effects are still less marked. Severe and moderate effects are observed in 17% of cases each with a dose of 0.4 mg./kilo; 13% with 0.6 mg./kilo. With a dose of 0.8 mg./kilo, however, marked effects were observed in 28%, moderate in 50%. The electrocardiographic changes while definitely less marked in the chronic stage than in the subacute, are definitely more marked than in the normal control group, 78% showing marked and moderate effects as compared to 27% in the normal control. Experiments in the chronic stage include animals with an infarct of 6 to 10 months' duration.

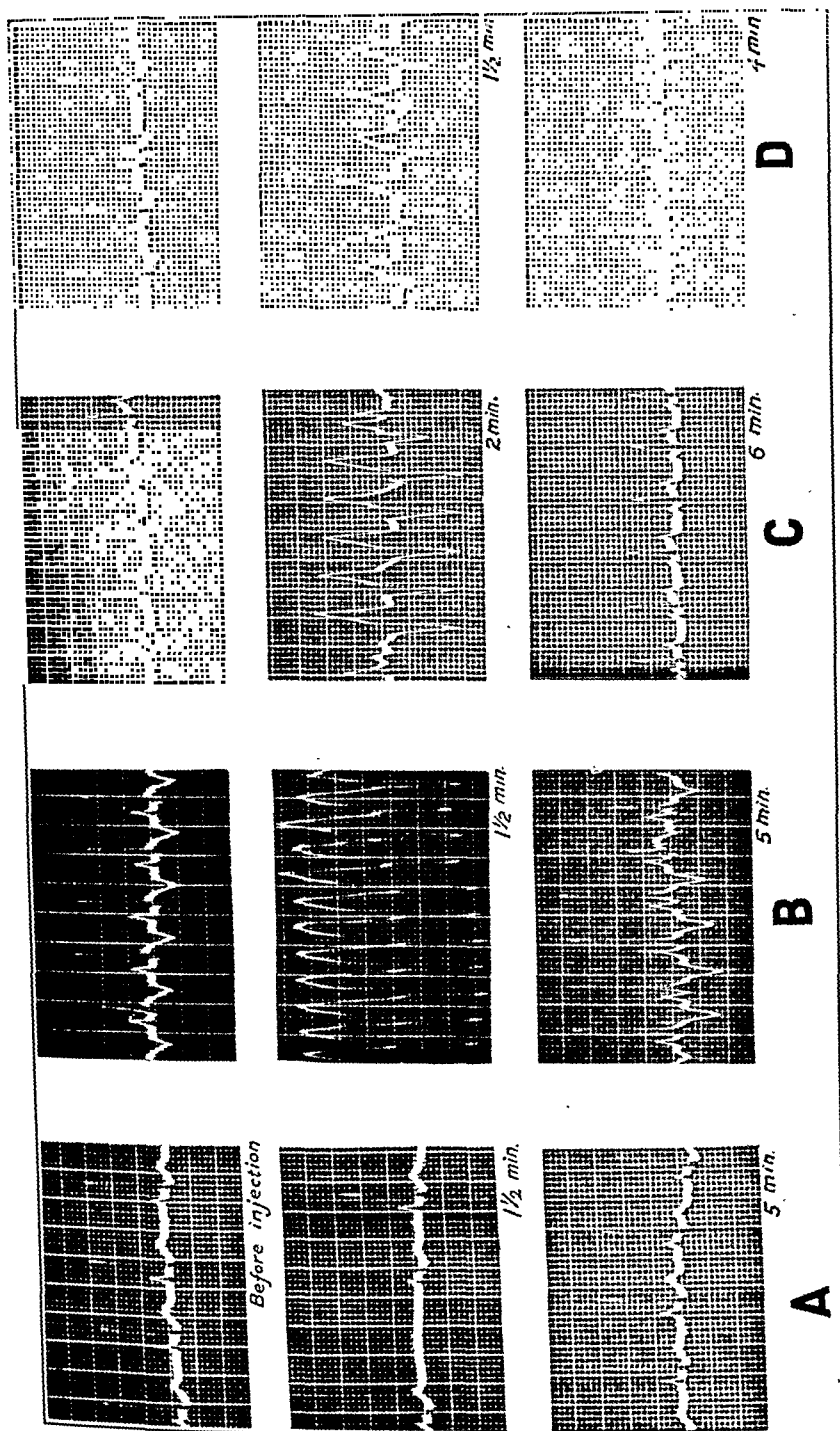


FIG. 2.—Dog 597, weight 10 kilos. All tracings taken in Lead II. A, Normal control before coronary ligation. Normal electrocardiogram. One and one-half minutes after 0.8 mg./kilo of nicotine, sino-auricular heart block, other effects slight. Five minutes later, return to normal. B, One day after coronary ligation, top electrocardiogram shows normal rhythm. One and one-half minutes after injection of 0.2 mg./kilo (one-quarter the dose given to normal control), ventricular tachycardia (marked effects lasting 3 minutes). At 5 minutes, simple tachycardia. C, Nine days after coronary ligation. Top tracing is control. Two minutes after injection of 0.4 mg./kilo, ectopic rhythm (nodal tachycardia?) (moderate effects); ST interval slightly elevated; record otherwise normal. Note less severe effects than those observed on the first day even though larger dose is given. D, Forty-four days after coronary ligation. Chronic stage of infarction. Top tracing is control. One and one-half minutes after 0.8 mg./kilo was injected, ectopic rhythm (nodal tachycardia?) lasting 2 1/2 minutes (moderate effects). At 4 minutes, slight tachycardia.

5 Days
0.2 mg/k

3 Days
0.2 mg/k

1 Day
0.2 mg/k

Control
0.6 mg/k

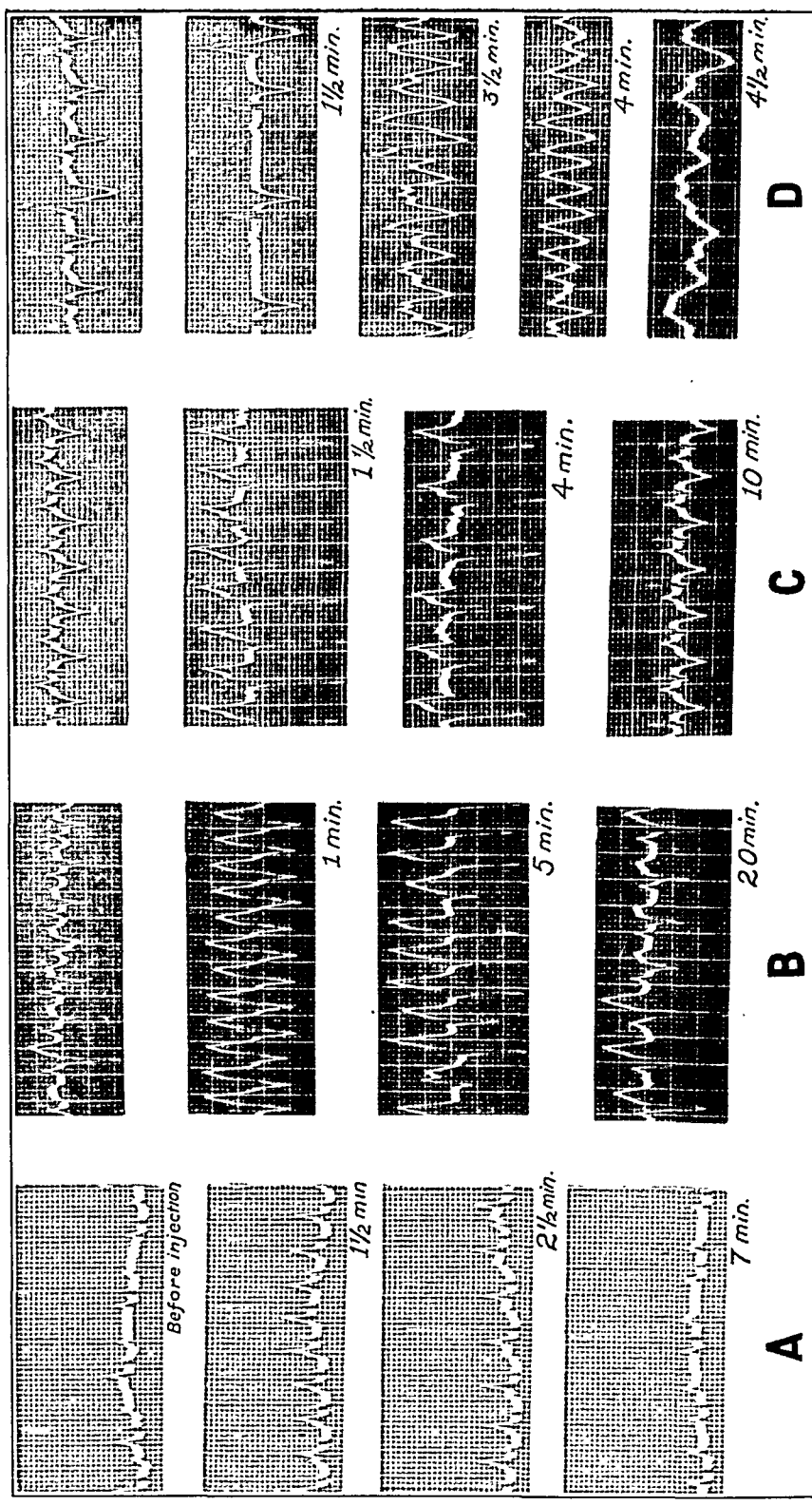


Fig. 3.—Dog 883, weight 13 kilos. All tracings taken in Lead II. In the normal dog (A) before injection of 0.6 mg./kilo of nicotine; normal electrocardiogram; at the height of the effects 1 1/2 minutes after injection, slight tachycardia. B, With 0.2 mg./kilo 1 day after coronary occlusion, ventricular tachycardia (rate about 300). C, On the third day the same dose produced marked effects with persisting tachycardia, probably nodal in origin. D, On the fifth day, after 0.2 mg./kilo, ventricular fibrillation, lasting 3 1/2 minutes.

Tolerance of Dogs to Nicotine. In testing the tolerance of dogs to nicotine, normal dogs were given a dose of 1.2 mg./kilo daily and the effects upon the electrocardiogram noted as in the previous experiments.

The results of four such experiments are shown in Figure 4. Marked effects following each dose were observed following the first 2 or 3 injections. Thereafter moderate changes were observed for 1 to 4 days and following daily injections for 7 or 8 days, the changes became slight and persisted as such during the remainder of the period of observation (11 days).

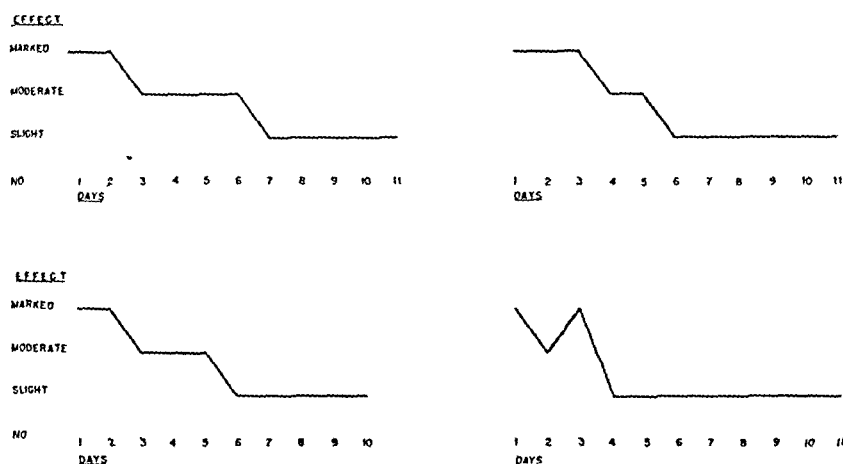


FIG. 4.—Tolerance experiments. In these four experiments, 1.2 mg./kilo was injected daily and diminution in the severity of the electrocardiographic effects noted as injections were continued (see text).

These experiments indicate that a diminution in the effect occurs rather rapidly following the daily administration of nicotine in the normal dog.

The relation of the experiments on tolerance to those previously discussed requires some discussion. The dose used in the tolerance experiments (1.2 mg./kilo) is a large one when given to an unanesthetized dog. It results not only in marked cardiovascular but severe systemic effects as well. Occasionally, a transient curare-like effect is produced. This dose was larger than the amounts given the experimental animals before and after myocardial infarction.* Moreover, in the animals with myocardial infarction, except for the first 3 to 4 days following coronary ligation, nicotine was not administered daily. One to 2 days intervened between experiments in the subacute and 1 week or longer in the chronic stage.

Nevertheless, some tolerance due to repeated administration of the nicotine must have occurred in the animals following coronary

* This dose was given in 5 experiments in normal animals but was not given in this large dose after myocardial infarction.

ligation, although it was probably much less than that found in the normal animals where large doses were administered daily.* This in itself, however, could not explain the lessened responses to nicotine, as the dog's infarct healed. Were we to rule out the effect of tolerance due to repeated administration of the drug in the acute and chronic stages of infarction, the diminution in the electrocardiographic effects obtained as healing of the infarction occurred, would be less marked than those recorded in our experiments. One other point is deserving of comment in this connection: When we speak of tolerance, we refer to the cardiac effects and more particularly to the electrocardiographic changes. This rapid alteration in tolerance observed in Table 2 does not necessarily refer to the other aspects of nicotine action, *e. g.*, upon the gastro-intestinal or respiratory systems. Even when there occurred marked diminution in the electrocardiographic effects, the respiratory and gastro-intestinal manifestations showed but little alteration from those initially observed.

Discussion. As to the mechanism underlying the difference in response to nicotine of normal animals and those with myocardial disease, there are several possible factors which may be offered in explanation. The most important cause responsible for severe effects following coronary ligation is probably increased cardiac work at a time when the heart is poorly able to accommodate the added strain. Nicotine is known to increase the work of the heart as a result of: (a) the increase in blood pressure by several different mechanisms; (b) by direct stimulating effect on the heart muscle through an adrenalin effect, and (c) increased strain resulting from the rapid cardiac rate as a result of sympathetic stimulation. In the stage of chronic infarction, the diseased area is replaced by a fibrous scar which is smaller in size than in the acute or subacute stage. While the effects mentioned above would also be operative here, they would be definitely less marked. The altered response to nicotine of injured muscle and injured nerve are probably additional factors in producing the increased effects.

Summary and Conclusion. Experiments were performed in normal animals and in animals in various stages of myocardial infarction following coronary ligation to study the cardiac effects following the inhalation of tobacco smoke and nicotine injection.

It was found that normal unanesthetized animals were able to tolerate a fairly wide range of dosage with the production of only slight electrocardiographic changes. Following myocardial damage produced by coronary ligation, marked electrocardiographic changes were obtained with a dose that was one-fourth of that required to produce only slight changes in the normal animal. These changes

* One of our dogs, used as a normal control for 6 months and given numerous injections during this period, showed no different reaction after coronary ligation than the typical experiments cited above.

became less marked as the subacute stage was reached, and were still less evident in the chronic stage of infarction. However, the electrocardiographic changes after equivalent doses were more marked in the stage of chronic infarction than in the normal controls. The factor of tolerance was considered and was shown not to materially influence these results. A parallel apparently existed between the degree of the electrocardiographic effects following the administration of nicotine and the severity of the myocardial damage.

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THE CONSTANCY OF ACTION OF PROTAMINE ZINC INSULIN.

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CLINICAL experience with protamine zinc insulin in the treatment of diabetes has suggested the probability that after a certain dose has been administered daily for several days it achieves a maximum intensity of action which is maintained with relatively little variation, not only from day to day, but from hour to hour. If it could be determined whether this probability is or is not a fact, it would serve to clarify our ideas concerning the mode of action of protamine zinc insulin and to explain certain characteristics in the behavior of the blood sugar incident to its use. The best approach to the problem seemed to lie in obtaining for comparison blood sugar time curves of about 13 hours' duration in diabetic patients receiving a daily injection of protamine insulin first at one time of day and then at another. If in a given case the curve resulting from the administration of the insulin, for example, in the morning differed greatly from that resulting from its administration in the evening, it would be apparent that the substance when given once a day is

not uniform in its action but has a peak of activity resembling, but of course more gradual in onset and of longer duration than, that of the quickly acting insulins. On the other hand, if the curves were similar, it could be concluded that protamine zinc insulin under these conditions exhibits no period of maximum effectiveness but exerts its influence in a fairly constant manner throughout the 24 hours.

Investigations based on these premises were carried out in the hospital in 8 patients with diabetes of different degrees of severity. The time-consuming nature of the studies made it necessary in most instances to choose as subjects patients whose medical or surgical complications required long periods of hospital care. No experimental observations were undertaken, however, until it seemed probable that the metabolic status had attained equilibrium, the complications having either disappeared or reached a point where they would not be expected to change sufficiently during the experiment to affect the diabetic state. In each case, diet, insulin dosage and, with one exception, activity were unaltered throughout the experiments. Since it is well known that even with all controllable factors kept constant the diabetic patient may vary considerably from day to day with respect to the behavior of his blood sugar, data for several days on a given régime were secured for comparison with data for a similar period on another régime, on the assumption that the averaged figures for each period would be more representative than the data from any single day of that period. It must be recognized, of course, that this method, although avoiding the confusion caused by wide daily fluctuations of the blood sugar, runs the risk that, precautions notwithstanding, variations in the disease itself may occur from one period to another, especially in severe cases, and thus render the interpretation of results a matter of difficulty.*

In detail, the procedure was as follows: On or soon after admission to the hospital the patient was placed on a weighed diet which was maintained for the duration of the investigation. The food was served at the usual hours and, excepting a single meal, was completely consumed in every case. For at least 3 days (preliminary period) before the beginning of any experiment the patient received a certain dose of protamine zinc insulin. The experiment was then started and during the first period of observation the same dose was administered for several days at the same time as in the preliminary period (for example, 7.30 A.M.) so that the collection of samples for blood sugar could be started at once. At the beginning of the second period, which was similar in length, the time of administration was changed (*e. g.*, to 8 P.M.), but either collections

* That such variations do occur is illustrated by Cases 1 and 5. In both of these cases of severe diabetes the evening curve seemed to differ from the preceding morning curve by a greater margin than the presumption of a constant action of insulin would permit. A second morning curve was therefore obtained and in neither case did it duplicate the first at all points, even though the experimental conditions were, as far as could be determined, identical.

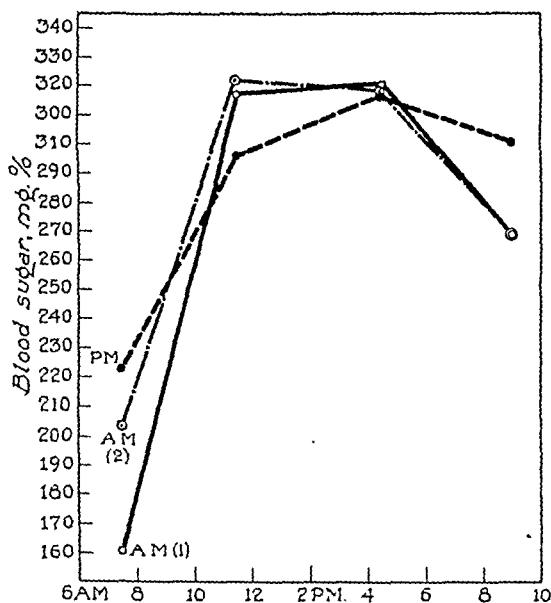


CHART 1.—Case 1. Patient O. M. Male, age 50. Duration 18 mos.; severe. Complications: (1) Congestive heart failure; compensation restored before experiments were begun. (2) Hemachromatosis with very large liver. Diet: C 200, P 60, F 90. Insulin: 35 P.

In all charts except Chart 7, curves labeled A.M. are those obtained when protamine zinc insulin was given in the morning; those labeled P.M. are those obtained when protamine zinc insulin was given in the evening.

Date.	Blood sugars.				24 hr. excretion.
	7:30.	11:30.	4:30.	9:00.	
9/6/39 . . .	Begin 35 P each morning				
9 . . .	81	259	300	217	19
10	344	366	323	51
11 . . .	242	352	273	244	29
12 . . .	83	269	319	245	15
13	353	344	297	21
14 . . .	217	314	337	307	22
15 . . .	196	341	293	246	20
16 . . .	109	289	313	259	15
17 . . .	232	334	334	278	25
18 . . .	117				
Average . . .	160	317	320	268	24
18 . . .	Begin 35 P each evening				
21 . . .	283	225	314	289	30
22 . . .	227	335	338	303	32
23 . . .	211	302	283	269	27
24	306	309	333	49
25 . . .	209	291	315	309	61
26 . . .	225	316	335	297	68
27 . . .	184				
Average . . .	223	296	316	300	45
27 . . .	Begin 35 P each morning				
29 . . .	169	322	326	288	63
30 . . .	213	304	263	186	34
10/1 . . .	150	288	330	289	68
2 . . .	267	355	340	305	53
3 . . .	217	340	326	271	40
Average . . .	203	322	317	268	52
					53

were not made, or results, if obtained, were discarded until 3 or 4 days had elapsed so as to permit reestablishment of equilibrium. In most cases the period of morning administration preceded that of the evening, but in some the reverse was true. In 2 cases a supplementary dose of regular insulin was given daily at 7.30 A.M.,

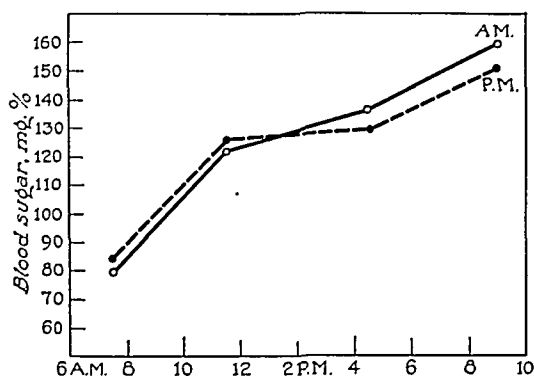


CHART 2.—Case 2. Patient J. K. Female, age 66. Duration 15 years; moderately severe. Complications: Amputation of leg for gangrene 5 weeks before experiments. Slow healing by granulation. No fever. Diet: C 100, P 60, F 150. Insulin: 35 P

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
35 P at 8:00 P.M.	84	126	129	151
(average of 5 days)				
35 P at 7:30 A.M.	80	122	136	159
(average of 8 days)				

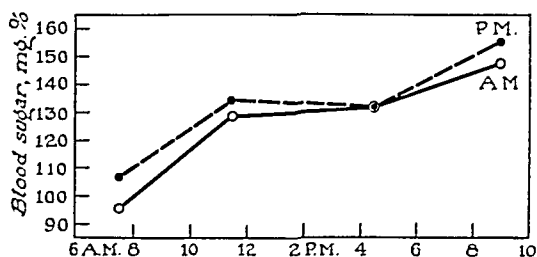


CHART 3.—Case 3. Patient M. W. Female, age 60. Duration 14 years; moderately severe. Complications: Carbuncle of back, completely healed before first experiment. Diet: C 100, P 60, F 150. Insulin: 30 P.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
30 P at 7:30 A.M.	96	129	132	148
(average of 7 days)				
30 P at 8:00 P.M.	107	134	132	155
(average of 6 days)				

regardless of the time of administration of the protamine compound. Specimens for blood sugar were taken, with few exceptions, four times daily: at 7.30 and 11.30 A.M. and 4.30 and 9 P.M.* The data are shown in the accompanying tables and charts.

* Blood was drawn from the finger tip and analyzed for sugar by the method of Miller and Van Slyke.²

Results. In 3 patients (Cases 2, 3 and 7) of 8 studied, the administration of protamine zinc insulin in the evening resulted in blood sugar curves practically identical with those observed during the morning administration. In 4 (Cases 1, 4, 5 and 6) of the remaining 5 patients the differences between the morning and evening curves

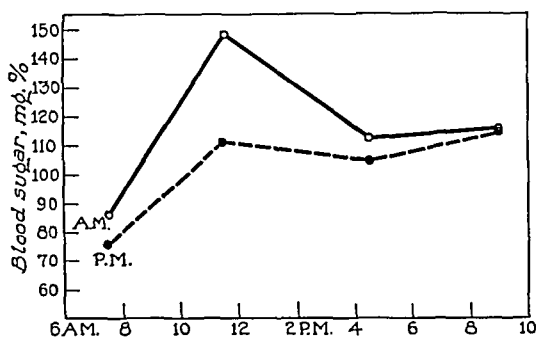


CHART 4.—Case 4. Patient C. S. Male, age 50. Duration 10 months; moderately severe. Complications: Low grade osteomyelitis of foot. No fever. Diet: C 200, P 63, F 90. Insulin: 35 P.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
35 P at 7:30 A.M. (average of 12 days)	86	148	112	115
35 P at 8:00 P.M. (average of 7 days)	76	111	104	114

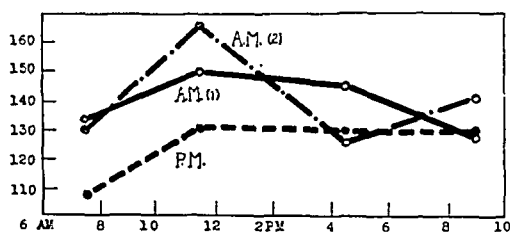


CHART 5.—Case 5. Patient H. L. Male, age 52. Duration 6 months; severe. Complications: (1) Neuritis, marked weakness. (2) Arteriosclerotic heart disease, compensated. (3) Insulin allergy requiring intramuscular injections. (4) Muscle biopsy 4 days before first experiment—no infection or fever. Diet: C 102, P 72, F 180. Insulin: 35 P + 15 R.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
35 P + 15 R, 7:30 A.M. (average of 6 days)	133	150	145	127
35 P, 5:00 P.M.; 15 R, 7:30 A.M. (average of 5 days)	107	131	129	129
35 P + 15 R, 7:30 A.M. (average of 6 days)	131	166	126	140

are slight and since they do not lie consistently in one direction are probably to be explained on the basis of variations in the state of the diabetes from week to week, rather than by the superiority of one régime over another. It is especially significant that in the 2 patients (Cases 5 and 6) in whom both the quickly and slowly

acting insulins were used, the regular insulin, given always before breakfast, had approximately the same effect, whether the protamine zinc insulin was injected at the same time or many hours later. The patient in Case 8, who had been known to us for more than a year as an unstable, juvenile diabetic, exhibited a much lower curve when she received her dose in the evening than in the morning. The experiment was invalidated, however, by the fact that early in the second (morning) period, and unknown to us at the time, the patient developed an infection in a thumb as a result of a lancet wound, so that no conclusions can be drawn in this case. Unfortunately, we were unable to make further observations after the infection subsided.

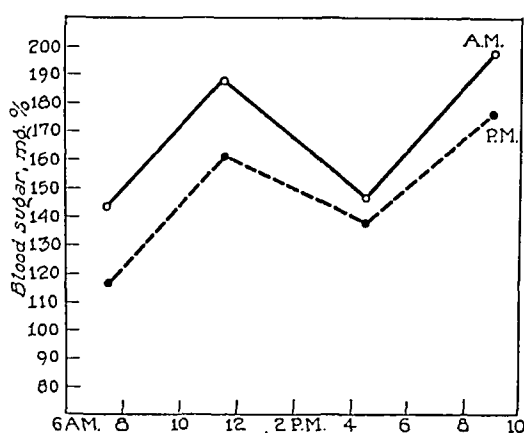


CHART 6.—Case 6. Patient G. E. Female, age 50. Duration 11 months; severe. Complications: (1) Mitral stenosis, well compensated. (2) Mild recurrent hyperthyroidism controlled by iodine. B.M.R. from +6 to -6. Diet: C 100, P 60, F 150. Insulin: 40 P + 40 R.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
40 P + 40 R, 7:30 A.M. (average of 7 days)	144	188	146	198
40 P, 8 P.M.; 40 R, 7:30 A.M. (average of 6 days)	117	161	138	176

Comment. It is apparent in all cases in which satisfactory studies could be made that the effect on the blood sugar of protamine zinc insulin given in the morning is not significantly different from its effect when given in the evening. A similar conclusion has been reached independently by Mark,¹ using a somewhat different method.

It can be stated, therefore, as a general principle that the action of protamine zinc insulin when injected once every 24 hours is reasonably constant. Additional support for this statement is afforded by the results of further investigations in Case 7. After blood sugar curves had been obtained with protamine zinc insulin given first before breakfast and then after supper (Fig. 7, Curves

P.A. and *P.P.*), the observations were repeated using regular insulin (Curves *R.A.* and *R.P.*). Finally, all insulin was withheld for 2 days and during the next 3 days a fifth experiment was performed (Curve *X*) while the patient continued to eat as usual but still received no insulin. That the practical identity of Curves *P.A.* and *P.P.* is indeed due to the constant action of protamine

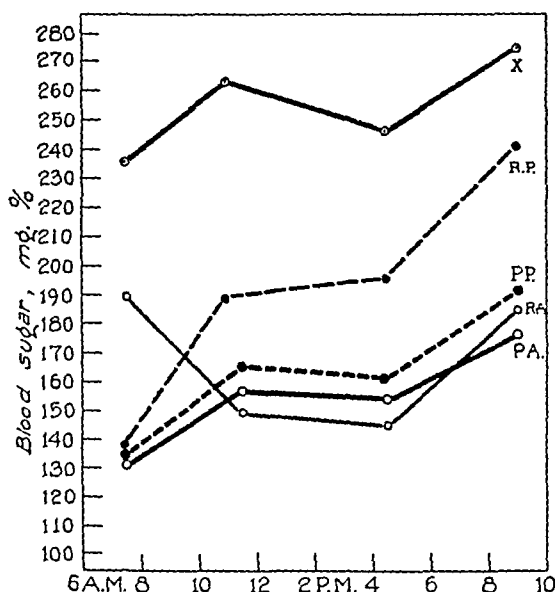


CHART 7.—Case 7. Patient E. N. Female, age 66. Duration 13 years; mild. Complications: (1) Hypertension. (2) Arteriosclerosis. (3) Angina pectoris, probably with coronary occlusion few weeks before admission. Diet: C 100, P 75, F 150.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
20 P, 7:30 A.M.	130	156	153	176
(average of 7 days)				
20 P, 8:00 P.M.	134	164	161	191
(average of 7 days)				
20 R, 8:00 A.M.	189	148	144	184
(average of 6 days)				
20 R, 8:00 P.M.	137	188	195	240
(average of 6 days)				
No insulin	235	263	246	274
(average of 3 days)				

P. A. = protamine zinc insulin given in the morning. *P. P.* = protamine zinc insulin given in the evening. *R. A.* = regular insulin given in the morning. *R. P.* = regular insulin given in the evening. *X* = no insulin.

zinc insulin rather than to other factors (*e. g.*, the "rhythmic function of the liver") is indicated by the marked difference in both shape and height between the morning and evening curves when a quickly acting insulin is employed (Curves *R.A.* and *R.P.*). The difference in shape, however, largely disappears after 11.30 A.M., suggesting that from this point on, since the timing and amount of the feedings were the same in all experiments, the congruity is

produced by endogenous influences. Particularly striking is the close similarity in contour with at the same time a great difference in height which exists throughout the day between the curve obtained with no insulin (Curve X) and the curves secured with protamine zinc insulin. Such a parallelism could result only from an influence which in the second instance modifies the spontaneous behavior of the blood sugar in a continuous and unvarying manner. It is probable that, at least in this patient, protamine zinc insulin serves chiefly to control the general *level* of the blood sugar curve, the *shape* of which is predetermined by endogenous factors operating in connection with the taking of food. Investigations now in

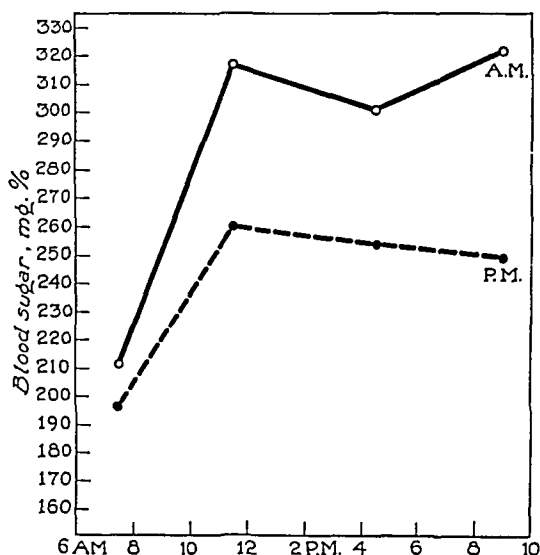


CHART 8.—Case 8. Patient E. B. Female, age 24. Duration 13 years; severe. Complications: (1) Periarticular fibrosis of left fourth finger, course stationary. (2) During second (morning) period, infection of thumb from lancet wound. Diet: C 150, P 60, F 57. Insulin: 25 P.

	Blood sugars.			
	7:30.	11:30.	4:30.	9:00.
25 P, 8:00 P.M.	196	259	253	248
(average of 10 days)				
25 P, 7:30 A.M.	211	317	301	322
(average of 8 days)				

progress indicate that this phenomenon occurs in patients with severe as well as those with mild diabetes.

The constancy of action of protamine zinc insulin holds several practical and theoretical implications: 1. It means that this form of insulin should no longer be regarded as having a period of maximum effectiveness. Although it is true that when given as a single dose to patients not receiving food it lowers the blood sugar to its minimum in from 12 to 18 hours, when used in the day-by-day treatment of diabetes it furnishes a continuous and relatively even supply of insulin from the subcutaneous depots. Its action,

once fully established, is maximal at all times. The patient, therefore can take his injections at whatever time of day is most convenient, provided that they are made 24 hours apart.

2. Protamine zinc insulin, administered daily, tends to stabilize the blood sugar during fasting at a certain level, the height of which depends upon the size of the dose. The blood sugar is pushed above this level by food during the day and gradually returns to it when the patient abstains from food during the night. If nocturnal hypoglycemia occurs it is not because of any greater intensity of insulin action at this time but because the amount is so large as to render the basic level too low. It is for this reason that the best criterion for the proper dose is the height of the fasting blood sugar.

3. In view of these considerations we cannot expect too much of the "new" insulin. As demonstrated in previous studies³ and substantiated by clinical experience, it controls the mild case of diabetes admirably, but in the severe case, even though it may render and maintain the blood sugar normal during fasting, it does not completely prevent hyperglycemia after a mixed meal. The resulting glycosuria can sometimes be avoided by distributing the dietary carbohydrate so as to include a midnight feeding, thus permitting some increase in the dose, but usually must be met by giving a supplementary quantity of quickly acting insulin before one or two of the daytime meals.

4. The fact that protamine zinc insulin, acting constantly throughout the 24 hours, controls mild diabetes very well but severe diabetes with difficulty suggests (a) that its chief function is to aid the pancreas in the regulation of the *endogenous* carbohydrate metabolism, (b) that, in accordance with a long-accepted but recently challenged theory (Soskin⁴), the ability of the body to handle *exogenous* carbohydrate depends to a considerable extent upon the response of the islets of Langerhans to the stimulus of carbohydrate ingestion, and (c) that such response is poor in the severe diabetic, better in the mild, and completely adequate in the normal individual.

Summary and Conclusions. 1. In 7 of 8 diabetic patients treated with protamine zinc insulin under carefully controlled conditions in the hospital, the behavior of the blood sugar through the daytime and evening hours was found to be essentially the same, whether the insulin was given in the morning or at night. Studies in the eighth case were vitiated by infection.

2. It is concluded that the action of protamine zinc insulin when injected once every 24 hours is relatively constant.

3. The practical and theoretical implications of this conclusion are discussed.

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TUBERCULOSIS IN THE ADOLESCENT.*

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ASCHOFF¹ gives tuberculosis at the age of puberty special significance by describing it as a transition form of phthisis with cranio-caudal extension and ulcerative destruction, the entire picture similar to phthisis of adults, but in contrast to the typical form of adult tuberculosis, the lymph nodes are markedly swollen, even though they do not show any great tendency to caseation as in children. Beitzke,² commenting on Aschoff's definition, says that although such transitions occur in puberty they are also seen up to the fifth decade of life and especially when phthisis shows a more subacute or acute form. According to Beitzke this form is well demarcated for the pathologist by Aschoff's description but it is challenged by the clinician who is not in the position to recognize its essential characteristics, *i. e.*, the strongly swollen, more or less caseous lymph nodes. The fact that this form is not exclusively found at puberty, but occurs, according to Redeker and Walter⁷ in other ages, has led the clinician to doubt Aschoff's justification of the term of puberty tuberculosis. Beitzke also claims that not only does this type of tuberculosis occur at the age of puberty, but nearly all disease forms of pulmonary phthisis are seen during this age period. Puhl,⁶ on the other hand, believes that puberty phthisis is characterized by a more exudative type of tuberculosis which runs a more malignant course; that hematogenous metastases are sometimes found and that the lymph nodes frequently show caseation, while in the lungs there are sharply expressed exudative processes with ulcerative breakdown.

A review of the literature of tuberculosis of puberty shows a diversity of opinion as to when puberty begins and when it ends. Whereas Aschoff makes no age demarcation of this period, Beitzke includes those cases which fall into the age group between 14 and 21 years, Stefko⁸ includes all cases between the age of 16 and 22 years, Falk⁴ includes the ages between 15 and 19 years, and still other individuals consider puberty to begin at the age of 12. In view of the lack of sharp delimitation of the age of puberty we have confined our study to the second decade of life, which will include many of the cases of tuberculosis at the age of puberty.

Material. Our own material consists of 100 consecutive autopsies of tuberculous individuals between the ages of 10 and 19 years performed at this hospital in a period of 5 years and 3 months.

* Presented before the Bureau of Tuberculosis, Department of Health, New York City, February 13, 1940.

During this period of time there were 1143 tuberculous autopsies so that 7% occurred during the second decade.

Sex. Sixty-seven of the 100 cases were females, 33 were males. This marked preponderance of females is borne out by the annual death rate of tuberculosis as compiled by the Department of Health of New York City. This is particularly interesting since in every other decade of life the ratio of male tuberculous autopsies to female tuberculous autopsies is 7 to 4. The reasons for this increased susceptibility of the female to tuberculosis during this decade is not entirely clear.

Color. Fifty-six of the 100 cases were negroes, 41 were white, while 3 were listed as Puerto Ricans. This ratio, also borne out by the annual death rate of the Department of Health in tuberculosis is also interesting. In every other decade of life above the age of 20 the proportion of whites to negroes is 7 to 4. The preponderance of negro autopsies during the second decade may in part be accounted for by the greater tendency of the negro to develop the progressive form of pulmonary tuberculosis and, secondly, that the primary complex which they develop in early life is more extensive and therefore the opportunity to develop hematogenous metastases with resultant extrapulmonary tuberculosis, particularly skeletal, is then much greater.

Pulmonary Lesions. The vast majority of cases (80) showed evidence of chronic pulmonary tuberculosis; in 13 there was a hematogenous tuberculosis of the lungs secondary to an extrapulmonary tuberculosis in the skeletal system or urogenital system. In 2 cases a progressive primary complex was present, while in 5, aside from a healed primary complex, the lungs were clear. In the latter 5 cases there was an associated active tuberculosis of the skeletal system or urogenital system.

Chronic Pulmonary Tuberculosis. The usual case of chronic pulmonary tuberculosis observed in adults is characterized by the presence of cavities in the upper parts of one or both upper lobes. These cavities are of moderate thickness and their walls are usually continuous with the visceral pleura in the apical and lateral aspects. The cavity walls generally become thicker as they grow older and, with the progressive increase in age, coal pigment is embedded within their walls. Also present in the upper lobes, and to a lesser extent in the lower lobes, are areas of fibrosis, encapsulated caseous foci; some of the latter contain calcium depositions and also acinous nodose foci. In those cases where death is due to a progression of the tuberculous process in the lungs, the most recent tuberculous process is located in the ventral and inferior portions of the upper lobes, antero-medial portion of the right middle lobe and the posterior aspects of the lower lobes. Fresh excavations are usually seen in the upper parts of the lower lobes. Isolated areas of lobular caseous pneumonia and acinous nodose foci are usually seen in these

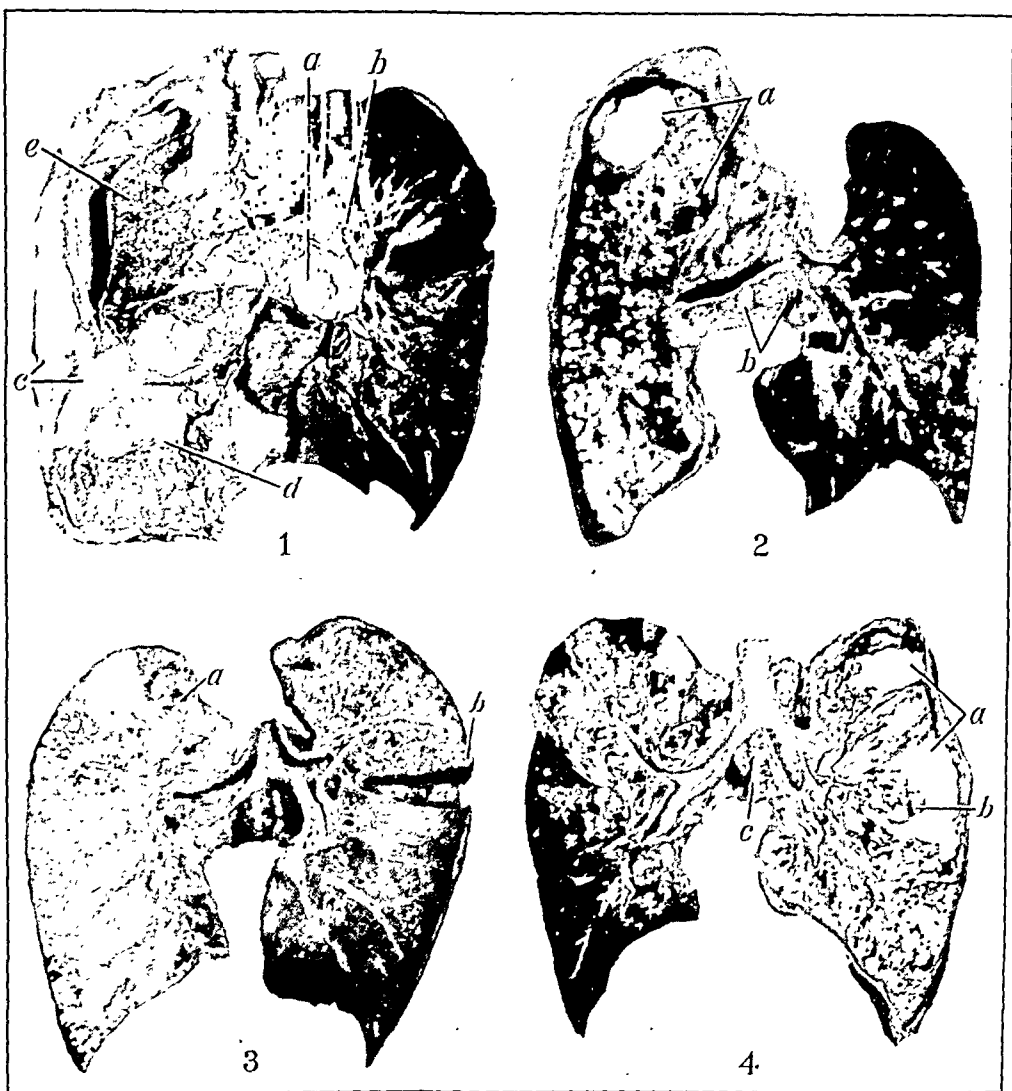


FIG. 1.—Coronal section of the lungs of a 16-year-old negro male (posterior view). The lymph node component (a) of the progressive primary complex is markedly enlarged, caseous and liquefied. (The primary focus not seen in this view is encapsulated and present in the right lower lobe.) The lymph node has perforated the right main bronchus (b). The pleuræ (c) over the left lung are extensively thickened by caseation. The caseous process has extended through the diaphragm (d). Caseous foci (e) are present in the compressed left lung.

FIG. 2.—Coronal section of the lungs of a 19-year-old negro female (posterior view). The left upper lobe contains large thin-walled excavations (a) lined by wide caseous zones. The remainder of the left lung and the right lower lobe contain confluent areas of caseous lobular pneumonia and acinous nodose foci. The inferior tracheobronchial lymph nodes (b) are enlarged and caseous.

FIG. 3.—Coronal section of the lungs of a 13-year-old negro female (posterior view). A fresh thin-walled excavation (a) lined by soft caseous particles is present in the left upper lobe. An extensive caseous lobular pneumonia occupies the greater portion of the remainder of the left lung. Fresh acinous nodose and caseous lobular foci (b) are present in the basal aspect of the right upper lobe.

FIG. 4.—Coronal section of the lungs of a 19-year-old female (posterior view). Excavations (a) present in the right upper and right lower lobes occupy a large portion of the lung. Trabeculae (b) representing obliterated pulmonary arteries protrude into the lumen of the cavity in the right lower lobe. Areas of caseous lobular pneumonia surround the cavities of the right lung and are present in the left upper lobe. The enlarged inferior tracheobronchial lymph nodes (c) show large areas of caseation.

recent spills. Massive areas of caseous lobular pneumonia are rarely observed in cases of chronic pulmonary tuberculosis in adults. This gradual progress from the upper portions of the lungs toward the base is characteristic of chronic pulmonary tuberculosis.

Although a number of the 80 cases showed lesions similar to those seen in adults, the majority of cases showed lesions of a more acute form. The cavities are usually more extensive and more numerous than one sees in later life. In one-half of the cases cavities are present in three or more lobes. The walls of the excavations are in most instances narrow and are lined by extensive areas of caseation. Another striking characteristic is the frequent presence in these cases of numerous areas of caseous lobular pneumonia and acinous nodose foci. In many of the former foci there are central areas of liquefaction. In some cases the caseous lobular pneumonia is so extensive that the lobe is solid. One is impressed by the lack of extensive fibrosis and lack of encapsulation of the caseous foci in these cases.

From the above findings we must conclude that, although in a number of cases the pulmonary tuberculosis is present in a chronic form, in most instances the course is a more acute one. We must agree with Beitzke, who pointed out that there is no characteristic phthisis for the age of puberty as Aschoff believed, but that the tuberculosis in puberty is a more severe form.

The apico-basal progression of the tuberculous process, characteristic for adult tuberculosis is also present in these cases.

The frequent finding of remnants of a healed primary complex, either in the lymph nodes or the lungs, or in both, is evidence of the fact that the chronic pulmonary tuberculosis, like that in adults, is the result of a post-primary superinfection.

In 13 of our cases there was a hematogenous dissemination to the lungs. Twelve of the cases had an associated tuberculosis of the skeletal system, genital or urinary system, while 1 showed an extensive tuberculous involvement of the ileum and cecum with extensive caseous involvement of the mesenteric glands.

In only 4 cases was there a typical generalized miliary tuberculosis characteristic of the older age groups. In the other 9 instances there were isolated foci of various ages and of various sizes. In those cases where there were only a few foci, their localization was in the apical aspects of the upper lobes.

The 2 cases of progressive primary complex present in this group occurred in negroes, a characteristic compatible with similar cases in early childhood. In both cases there was a marked enlargement of the primary focus and the lymph node component with a nodular dissemination to the parenchymatous organs.

Another finding which is rare in cases of chronic pulmonary tuberculosis over the age of 20 is the presence of caseous foci in the regional tracheobronchial lymph nodes. The presence of caseation

in these nodes was found in 29 instances of the 80 cases of chronic pulmonary tuberculosis. In a few cases the caseation was limited to one part of the tracheobronchial angle; in most instances, however, all the lymph nodes in this region were enlarged and almost completely replaced by caseation. The enlargement of the lymph nodes was so extensive in some instances that the diameter was

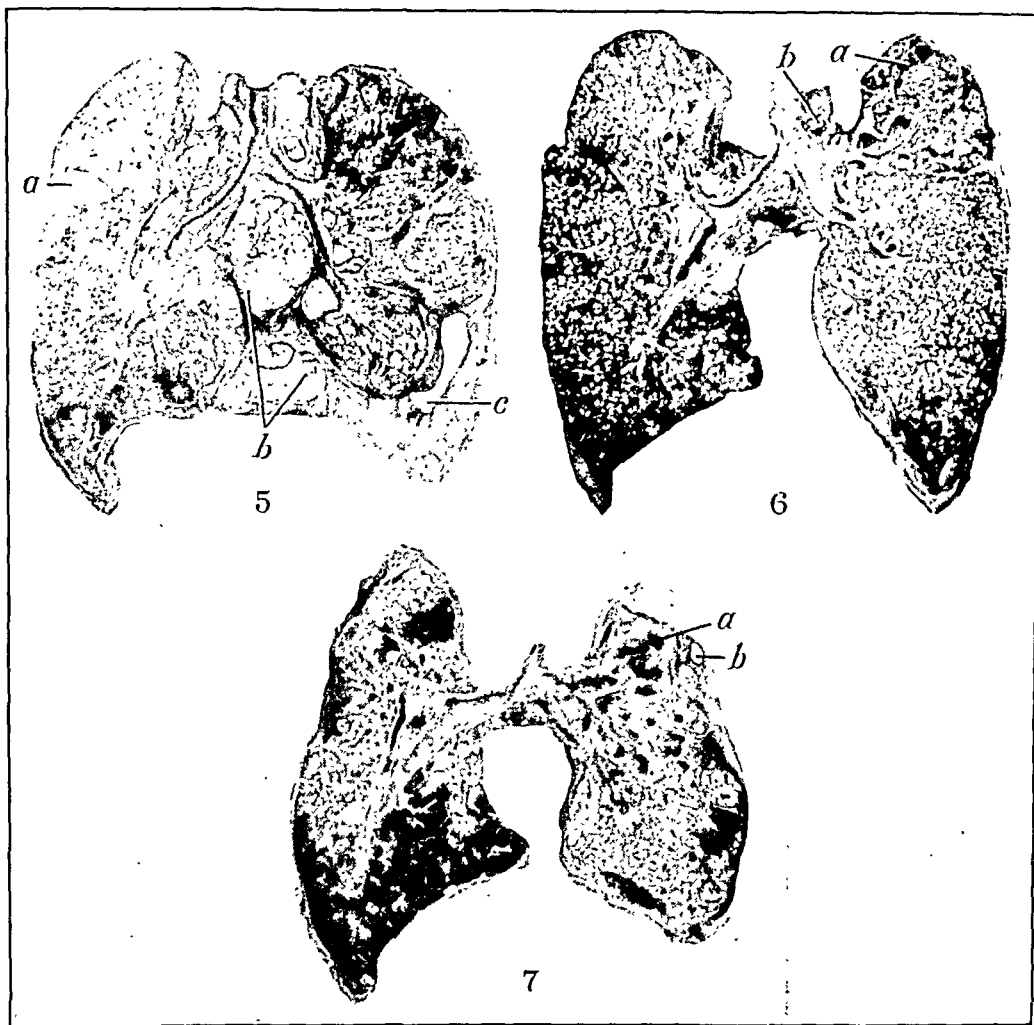


FIG. 5.—Coronal section of the lungs of a 16-year-old negro female (posterior view). A cavity present in the left upper lobe (*a*) is surrounded by an extensive confluent caseous lobular pneumonia. The tracheobronchial and mediastinal lymph nodes (*b*) are extensively enlarged and caseous. An empyema cavity (*c*) is present over the right lower lobe.

FIG. 6.—Coronal section of the lungs of a 13-year-old negro female (posterior view). A thin-walled cavity (*a*) is present in the right upper lobe. A diffuse acinous spread, resulting from repeated pulmonary hemorrhages, is present throughout both lungs. A calcified focus (*b*) present in the right superior tracheobronchial lymph node.

FIG. 7.—Coronal section of the lungs of an 11-year-old white male (posterior view). A chronic thick-walled excavation (*a*) is present in the right upper lobe. Acinous and caseous lobular foci are present in both lungs. A residual pneumothorax (*b*) is present over the right upper lobe.

sometimes 6 cm. in size. This enlargement resulted in a marked widening of the mediastinum and when the inferior tracheobronchial nodes were so involved they caused an extensive widening of the angle between the right and left main bronchi. The paratracheal glands and cervical glands were sometimes similarly involved. It is interesting to note that the involvement of the nodes by caseation occurred in negroes in 22 instances, in 2 of the 3 Puerto Ricans and in the whites in 6 cases. In all other cases the lymph nodes were enlarged, a characteristic which, although pointed out by Aschoff as a peculiarity of tuberculosis in the puberty age, is no different from tuberculosis in the older age groups.

The extension of the caseous process into the regional lymph nodes is an indication of the overwhelming process in the lungs. That this caseation most frequently occurs in the negro has been pointed out by Pinner and Kasper.⁵ We feel, however, that this caseous involvement of the lymph nodes, although seen frequently in the second decade, is infrequent in the higher age groups even in the negro.

Intestinal Tuberculosis. Cullen,³ in a recent study of intestinal tuberculosis at our institution, has pointed out that although the incidence for all ages is 70.4%, he found the highest incidence occurring in the age period between 10 and 19 years (78.5%). In this series of 100 cases we found intestinal tuberculosis in 76 instances (76%). Although in a few instances the tuberculous involvement was limited to the ileum or ileum and cecum, in the vast majority of cases the tuberculous process extended from the ileum, through the colon and, in some instances, extended from the jejunum to the rectum. The ulcers were of varying depths and sizes. From many of the deeper seated ulcers lymphatic drainage to the mesenteric lymph nodes could be followed.

The tendency to extensive tuberculosis of the intestines is an indication of the severity and acuteness of the process. It has been our experience that, generally, the more chronic the ulcerative tuberculous process in the lungs, the less tendency there is to intestinal tuberculosis and the less severe the tuberculous process, even in the presence of a positive sputum for many years.

Extrapulmonary Tuberculosis. In 23 cases an extrapulmonary tuberculosis was present. In 5 cases it was associated with chronic pulmonary tuberculosis. In 40 cases between the ages of 10 and 15 years there were 14 such cases (35%) which is an unusually high incidence, while in the remaining 60 cases between the ages of 16 and 19 years there were only 9 cases (15%). This sudden drop of extrapulmonary tuberculosis after the age of 15 years is not surprising. The development of tuberculosis in these enclosed systems is often directly dependent upon the development of the primary complex—as is seen in the frequent association of skeletal or genital tuberculosis in which a healed primary complex is the only other tuberculous lesion in the body. The development of the extrapul-

monary tuberculosis from the primary infection may be explained in the following manner. While the primary complex is still fresh, the caseous process in the lymph node drains into the venous circulation with a resultant hematogenous dissemination. What the factors are which limit the development of the tuberculous process to certain parts of the skeletal system, the spine, hip, and knee preferably, or in other cases to the genital system, is not known. That these hematogenous seedings are not limited to the extrapulmonary system, in which the tuberculosis develops, is seen in the presence of old pulmonary apical tuberculous foci in these cases. Here the primary complex, through encapsulation and calcium deposition, undergoes anatomic healing, while the tuberculous process developing in the extrapulmonary system gradually progresses. The tuberculous process is a slowly progressing one in the genital and urinary system, and even slower in the skeletal system. Since the occurrence of the primary complex rapidly declines after the age of 10, this rapid decline in extrapulmonary tuberculosis may be so explained.

The skeletal system was involved 13 times, once in association with female genital tuberculosis and twice in association with tuberculosis of the urinary tract. Tuberculosis of the female genital system was observed in 9 cases (13%) in contrast to the 9.1% in all age groups, while male genital tuberculosis was observed in 3 cases (12%), in contrast to 15% in all age groups. It is interesting to note that the incidence of female genital tuberculosis is greater than that of male genital tuberculosis in this decade, the reverse is true in the higher decades of life.

Conclusions. 1. In 100 consecutive autopsies on tuberculosis patients between the ages of 10 and 19 years there were 67 females and 33 males; this is in contrast to every other decade where the ratio of male to female tuberculous autopsies is 7 to 4.

2. There were 56 negroes, 41 whites and 3 Puerto Ricans in this group, in contrast to all higher decades where the ratio of negro to white autopsies is 4 to 7.

3. Eighty cases showed evidence of chronic pulmonary tuberculosis, 5 of which were associated with extrapulmonary tuberculosis, while in a small number of cases the pulmonary tuberculosis was of a chronic character similar to that seen in the older decades, the vast majority showing a more acute course characterized by the presence of numerous cavities of an anatomically recent nature, and also by the presence of extensive exudative lesions in the form of caseous lobular pneumonia and recent acinous nodose foci. Encapsulation of the caseous foci and fibrosis, evidence of a chronic character, were minimal in the majority of these cases: (a) there were 2 cases of a progressive primary complex; (b) the 5 cases which showed only a healed primary complex and the 13 cases with hematogenous disseminations in the lungs were associated with extrapulmonary isolated organ tuberculosis.

4. Twenty-nine of the cases of chronic pulmonary tuberculosis showed cessation of the tracheobronchial lymph glands, 22 of which occurred in negroes.

5. Intestinal tuberculosis occurred in 76% of these cases, the highest incidence of any decade. The severity and extent of intestinal tuberculosis are greater in this decade than in the higher decades of life.

6. There were 23 cases of extrapulmonary tuberculosis. There was an incidence of 35% between the ages of 16 and 19 years. The skeletal system was involved 13 times, female genital system in 9 instances, male genital system in 4 and the urinary tract 3 times.

7. Although one is not justified in designating tuberculosis occurring in this decade as puberty tuberculosis, yet we may conclude that tuberculosis occurring in the second decade of life shows a high incidence of extrapulmonary tuberculosis, particularly up to the age of 15, and that chronic pulmonary tuberculosis occurring in this period is of a more acute form than that occurring later in life. Why this fact is so, we are not prepared to say.

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THE COURSE OF THE PLASMA PROTEIN CHANGES IN EARLY LYMPHOPATHIA VENEREUM UNDER TREATMENT WITH SULFANILAMIDE.

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INCREASE in the globulin content of the blood with concomitant decrease in albumin and consequent increase in total protein and reversal of the albumin-globulin ratio has been reported in lymphopathia venereum by a number of authors.^{6,9,10,16} Comparison of the blood protein values in normal and infected individuals, as presented in Tables 1 and 2, demonstrates that this chemical derangement is uniform and usually of marked degree. Peters and Eisenman¹⁴ consider 6 to 8 gm. of protein, 4 to 5 gm. of albumin, and 1.4 to 3 gm. of globulin per 100 cc. serum the normal range.

The many forms of treatment which have been recommended for use in lymphopathia venereum testify to the inadequacy of all past modes of therapy. Radical excision, repeated aspiration, Roentgen

irradiation, and local injections of various kinds into the early lymph node lesions, have had their advocates. Intravenous injections of Lugol's solution, sodium iodide, arsenicals, copper ammonium sulphate, various gold salts, sodium salicylate, tartar emetic, and Frei antigen have been recommended. However, uniformly effective results have not been achieved by any method thus far advanced.

The advent of sulfanilamide reawakened the interest of a number of workers searching for an efficacious therapy for lymphopathia venereum. Levaditi and Vaisman¹¹ treated a single monkey inoculated intracerebrally with lymphopathia venereum with "Rubiazol," one of the sulfanilamide group. The authors felt that the drug was ineffective. Bär¹ studied the effect of prontosil album on mice infected intracerebrally with lymphopathia venereum, and concluded that it was of value in prolonging the life of the infected animals. In a later study, Schlossberger and Bär¹⁷ report that brains of infected mice treated with sulfanilamide can transmit the infection by transfer, and conclude that the drug exerts only an inhibitory action on the virus, but that the resistance of the body tissues determines whether the infection is cured.

A number of studies have been reported in human lymphopathia venereum. Shaffer and Arnold¹⁸ treated 22 negroes suffering from lymphopathia venereum with sulfanilamide. Five had had the disease less than 3 months; 6, 3 to 12 months; and 11 over 1 year. Four patients were apparently cured, 11 were markedly improved, and 3 did not respond. Four patients disappeared from observation. Shropshear¹⁹ reports marked improvement, as evidenced by gain in weight and disappearance of blood and pus from the stools, in 9 patients with rectal strictures treated with sulfanilamide. Three additional male patients with inguinal adenitis were favorably influenced, but the lesions did not completely subside under treatment. Gjuric⁵ attained good results in 23 patients with inguinal adenitis by treatment with prontosil album plus Fuadin, an antimony preparation. Early results were also favorable in a few patients treated with prontosil album, prontosil soluble, or Uliron alone. In 15 patients with inguinal adenitis, Hamilton⁸ reports 13 complete symptomatic cures following sulfanilamide treatment. Eighty grains were administered for 2 days, 60 gr. for 3 days, and then 40 gr. for 4 to 8 additional days. Recurrences were noted in 2 patients. Earle⁴ treated 2 male patients with bilateral inguinal adenitis with sulfapyridine, 3 gm. per day for 6 and 8 days, then 2 gm. per day for 3 and 6 days, and achieved clinical cure in 11 and 14 days. Nair and Chetty¹³ treated 15 cases of early adenitis and 5 with rectal stricture due to lymphopathia venereum with prontosil rubrum, 2 to 2.5 gm. per day for 5 to 6 days, then after an interval of 4 to 5 days, 2 gm. per day for 3 additional days. In some of the patients, Fuadin was also used. All the early cases were cured

rapidly, and the patients with rectal strictures achieved symptomatic relief. Marino and his coworkers¹² report a single case of inguinal adenitis treated successfully with sulfanilamide, as well as 2 cases with rectal stricture.

Thus, it has been established that a marked hyperglobulinemia is an almost constant finding in patients suffering from lymphopathia venereum, and growing evidence indicates that sulfanilamide and its related compounds bid fair to be recognized as the first effective mode of therapeusis in this disease. It was felt that a correlation between the clinical effects observed in early lymphopathia venereum under treatment with sulfanilamide, and the changes in the plasma protein picture, might throw some light on the causation and mechanism of the alterations in the blood chemistry.

TABLE 1.—DETERMINATIONS OF BLOOD PROTEINS (GM. PER 100 CC.) IN NORMAL INDIVIDUALS.

Author.	Fraction.	No. of individuals tested.	Protein.			Albumin.			Globulin.			A/G ratio.		
			Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.
Peters and Van Slyke ¹⁵	Plasma	32	7.96	6.34	7.01	5.24	3.77	4.40	3.55	1.96	2.63	2.23	1.38	1.67
Rosen et al. ¹⁶	Serum	33			6.66			4.38			2.28			
Howard et al. ⁹	Serum	24	7.37	6.29	6.88	5.37	4.66	4.98	2.31	1.35	1.96	3.70	2.00	2.60

Material Studied. Twenty unselected patients with early lymphopathia venereum, characterized by unilateral or bilateral inguinal adenitis, were treated with sulfanilamide. Plasma total protein, albumin, and globulin determinations were made before the start of treatment and at intervals thereafter. The macro-Kjeldahl method was used.*

All of the patients were negroes, 16 males and 4 females. Their ages ranged from 13 to 34 years. Twelve had syphilis in addition to lymphopathia venereum, and of these, 3 presented chancres on admission, 2 had secondary syphilis, 1 had early latent syphilis, and 6 had late syphilis. Eight patients were non-syphilitic. One patient (Case N) had active pulmonary tuberculosis for which she was institutionalized 2 weeks after beginning treatment, and 1 patient (Case E) became pregnant about 1 month after starting treatment.

All patients were subjected to Frei and Ito-Reenstierna intracutaneous tests.† In most cases, the tests were made before treatment was instituted. For the purpose of comparing and evaluating

* All tests were performed in the Biochemical Laboratory of the Johns Hopkins Hospital, under the direction of Dr. Mary Buell.

† I am indebted to Dr. H. M. Robinson, Sr., for the performance and reading of the intracutaneous tests.

different Frei antigens from human sources, at least 5 human antigens were used in each case. In addition, a mouse brain Frei antigen was used in most of the patients. The D'Melcos bacillary chancroidal antigen was routinely used, and in addition, the Ducrey antigen, prepared in this country, was utilized in some of the patients. All tests were read after 48 hours. An indurated papule 5 mm. or more in diameter, surrounded by an erythematous zone, was considered a positive reaction. A similar papule 4 to 5 mm. in diameter was read as doubtful. Any smaller reaction was called negative. Twelve patients had frankly positive Frei tests and negative chancroidal tests. Four gave doubtful Frei and negative Ito-Reenstierna, 1 was positive to both, 1 doubtful to both, 1 positive

TABLE 2.—DETERMINATIONS OF BLOOD PROTEINS (GM. PER 100 CC.) IN PATIENTS WITH LYMPHOPATHIA VENEREUM.

Author.	Stage of disease.	Fraction.	No. of individuals tested.	Protein.			Albumin.			Globulin.			A/G ratio.		
				Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.	Mean.
Gutman et al. ⁶	All stages	Serum	35	11.20	6.80		4.70	2.30		8.30	2.20				
Rosen et al. ¹⁵	Adenitis	Serum	45			7.55			4.02			3.53			
Rosen et al. ¹⁵	Rectal stricture and esthiomene	Serum	39			7.91			3.67			4.24			
Howard et al. ⁹	Adenitis	Serum	19			8.04			4.15			3.88			1.10
Howard et al. ⁹	Healed adenitis	Serum	27			7.37			4.42			2.95			1.60
Howard et al. ⁹	Rectal stricture, proctitis, and esthiomene	Serum	35			8.25			3.49			4.76			0.70
Kampmeier et al. ¹⁰	All stages	Serum	67	11.77	6.84		6.44	2.51		9.09	1.13		5.75	0.33	
Present study*	Adenitis	Plasma	20	9.51	7.42	8.28	5.39	1.86	3.66	6.22	3.03	4.62	1.78	0.32	0.83

* Initial determination only.

to Frei and doubtful to Ito-Reenstierna, and 1 had a doubtful Frei and a positive Ito-Reenstierna. Thus, in 16 of the 20 cases, immunologic evidence supported the clinical diagnosis of lymphopathia venereum as opposed to chancroid, and in no patient was a negative Frei test observed.

On admission, 4 patients presented small primary lesions of lymphopathia venereum on the genitals, 1 gave a history of a lesion, and in 2 of the patients with primary syphilis it could not be determined whether the penile ulcer represented a combined syphilitic and lymphopathia venereum infection. Fourteen patients gave no history and showed no evidence of a primary lesion. In 2 female patients (Cases A and E), unilateral edema of a labium majorum was noted, though no primary lesion was evident; and 2 patients (Cases A and

B) had constitutional symptoms and fever (99.8° and 101.4° F. (oral) respectively) on admission. Six patients had right inguinal node involvement, 7 left, and 7 bilateral involvement. On institution of sulfanilamide treatment, 8 patients presented non-fluctuant nodes, 5 were fluctuant, and 7 were already draining pus, following spontaneous rupture, aspiration, or incision. The stated duration of the lymph node inflammation when treatment was begun ranged from 4 to 72 days, the mean duration being 29.5 days. Complete physical examinations revealed no evidence of lesions of lymphopathia venereum other than the above.

The initial dose of sulfanilamide was 3 to 4.5 gm. per day, and the higher dosage was cut to 3 gm. per day after 2 to 5 days, depending on the individual response to treatment. The patient was instructed to take his sulfanilamide tablets in four equal doses at 7 A.M., 12 NOON, 5 P.M., and 10 P.M. One gram of sodium bicarbonate in tablet form was administered with each dose. The following printed instructions were given to each patient:

- (a) Drink little water, not more than 4 glasses a day. Do not drink any beer, wine, gin or any type of liquor while you are taking the medicine.
- (b) Stay out of the sun. If you go out on a sunny day, wear a hat and keep your arms covered.
- (c) You may get dizzy or feel sick at your stomach after taking the medicine. If you do, lie down and be quiet, but continue taking the pills as directed.
- (d) If your eyes or skin get yellow, if you break out in a skin rash, if you start vomiting or get chills and fever, *stop* taking the pills and return to see the doctor the following morning.

In some cases presenting fluctuant lymph node abscesses on admission, aspiration was carried out, and some of the patients used hot compresses at home. No other treatment was utilized.

The total dosage of sulfanilamide per patient ranged from 9 to 120 gm., the total treatment period from 2 to 42 days. All patients were ambulant while under treatment. Patients were usually observed twice a week for the first 2 weeks, and then once a week, and on each visit, were questioned regarding reactions to treatment and examined to determine the status of the disease. Plasma protein, albumin and globulin determinations were made every week at first, and at longer intervals later on. Sixteen of the 20 patients studied were followed up by a home visit 102 to 325 days after institution of treatment. An interim history was taken, an examination made, and a specimen of blood taken for plasma chemistry studies.

Treatment Reactions. One case (T) developed a fixed eruption after 2 days, which necessitated discontinuation of treatment. This patient had received sulfanilamide without incident 1 year before, following acute rheumatic fever. Two patients (D and Q) probably developed hemolytic anemia as a result of the use of sulfanilamide,

the hemoglobin dropping in 6 and 10 days to 7.8 and 8.6 gm. respectively. In each case, treatment was immediately withheld and the patient recovered uneventfully.

The following complaints were elicited from 10 patients within 1 to 14 days after starting treatment: Headache in 6, drowsiness in 5, vertigo in 4, mental clouding in 3, nausea in 2, weakness in 2, and dyspnea, palpitation and anorexia in 1 each. Seven patients had no untoward reaction to treatment, and no data on this point were available in 1 patient. In none of the cases were these minor symptoms severe enough to necessitate cessation of treatment.

Clinical Results of Treatment. Relief of pain and tenderness within a few days after beginning treatment was the most striking therapeutic effect noted. "When I take those pills it don't hurt no more when I walk" (3 days' treatment), "I haven't noticed that knot since the day after I started taking the pills," "I feel 100 per cent better" (7 days' treatment), "Knot seems to have gone away" (3 days' treatment), are some of the statements recorded on the charts. Examination of these patients a few days after the beginning of treatment often showed absolutely no change in the dimensions or degree of induration of the lymph node, even though the patient was enthusiastic about the results of treatment. In almost all cases, it was noted that resolution of the inflammatory mass was a matter of weeks, whereas relief of pain in the favorable cases occurred in a few days. Thus, the patient's own estimate of his progress toward cure antedated that of the physician, and a number of the cases discontinued treatment while inflammatory activity was still present. In the 2 febrile patients with constitutional symptoms, temperature was reduced to normal and malaise disappeared in 2 and 5 days.

Fourteen of the 20 patients studied experienced rapid and marked amelioration of symptoms and signs, and 11 of these were classed as symptomatically cured at the time treatment was discontinued, although objective signs, such as enlargement or adherence of the lymph nodes, or induration and thickening of the skin, remained in all but 2 cases. Two of these 11 patients (K and H) clearly demonstrated that improvement under treatment was not simply coincidental. The inguinal lesions responded rapidly to sulfanilamide, which was discontinued when the adenitis had almost completely regressed. In each case, in 17 and 21 days respectively after treatment was stopped, the adenitis reappeared and was, surprisingly, resistant to further treatment. In the 3 additional cases, the patients considered themselves well and discontinued treatment, although inflamed, enlarged, but non-tender lymph nodes were still present.

Six patients were classed as treatment failures. Cases I and J were uncoöperative, received treatment for only 2 and 3 days respectively, and were not improved. Case T, who had a fixed eruption

and hence received only 2 days' treatment, and Case Q, who developed hemolytic anemia after 7 days of therapy, also were not improved. Two patients (A and R) are listed as unexplained treatment failures in that their lesions progressed while they were apparently receiving adequate therapy.

On follow-up of the 16 accessible cases 102 to 325 days after the start of treatment, 12 immediate treatment successes and 4 immediate treatment failures were reexamined. Of the 4 patients re-studied who had not improved under treatment, 1 (Case I) had had a recent frank acute exacerbation of his lymphadenitis and still presented inflammatory activity, and 3 showed persistent residua without symptoms. Of the 12 cases which had responded well to treatment, 10 patients gave no history of recurrence of adenitis and showed no residua in the inguinal region. However, 1 of these (Case G) complained of intermittent urethral discharge without dysuria for 6 months, beginning 4 months after treatment. It was felt that this might be a Waelsch type of urethritis caused by the virus of lymphopathia venereum² and this case was considered to have had a clinical relapse. The 2 remaining patients, H and K, in the immediate treatment success group were those noted above as relapsing when treatment was stopped prematurely. On follow-up, each still presented residual induration without symptoms.

To recapitulate, 14 of the 20 patients responded rapidly to treatment, and 2 of these relapsed because of premature withdrawal of the drug. On reexamination, 102 to 235 days later, of 12 of the 14 successfully treated patients, 9 showed no residua, 2 had residual induration, and 1 a mild urethritis, possibly caused by lymphopathia venereum. Reexamination of 4 of the 6 treatment failures revealed inflammatory activity in 1 and residua in 3. Table 3 tabulates the relevant data in the entire group of patients.

Plasma Proteins. Seventy-two complete plasma protein determinations were made on the 20 patients. In 1 case only one complete report was obtained, and in 1 patient 9 determinations were made. In the entire group, the initial protein values ranged from 7.42 to 9.51 gm., and the mean was 8.28 gm. per 100 cc. of plasma. Fourteen of the 20 were above 8 gm., the upper limit of normal.¹⁴ Initial albumin values were 1.86 to 5.39 gm., mean 3.66, and 14 of the cases were below 4 gm., the lower limit of normal. The first globulin determination varied from 3.03 to 6.22, mean 4.62, and no case fell within the normal limits of 1.4 to 3 gm. The albumin-globulin ratio ranged from 0.32 to 1.78, mean 0.83.

The chemical determinations on Case N were excluded from the graphic analyses. This patient had active pulmonary tuberculosis and still presented a marked hyperglobulinemia 10 months after her inguinal adenitis had completely disappeared. It was felt that her plasma protein changes were caused by tuberculosis, rather than by lymphopathia venereum.

TABLE 3.—CLINICAL DATA ON 20 NEGROES WITH EARLY INGUINAL ADENITIS OF LYMPHOPATHIA VENEREUM TREATED WITH SULFANILAMIDE.

Case.	Age.	Sex.	Adenitis.		Frei test. ²	D'Meleos test. ²	Number of days under treatment.	Total amount sulfanilamide given (gm.).	Improvement.		Reaction to treatment.		Observation period (days after start of treatment).	Favorable response to treatment.	Activity status at end of observation period. ³
			Duration before treatment (days).	Status before treatment. ¹					Days after treatment started.	Type of improvement. ³	Days after treatment started.	Type of reaction. ⁴			
A	18	F	4	NF	2	0	16	57	2	T↓, I↓	1	H	123	No	±
B	23	M	11	NF	4	0	37	103	7	TO, FO	..	None	147	Yes	0
C	17	M	14	NF	4	0	20	88	2	T↓, FO	..	None	212	Yes	0
D	23	M	14	NF	4	0	6	21	5	TO	6	H.A.	302	Yes	0
E	13	F	17	NF	4	0	42	87	6	I↓	..	None	164	Yes	0
F	22	M	17	NF	2	0	15	50	3	T↓, I↓	..	None	102	Yes	0
G	26	M	28	NF	2	0	21	73	3	TO	7	H	279	Yes	± ⁶
H	30	M	28	NF	4	2	26 ⁷	90	5	T↓	4	DHM	233	Yes	±
I	31	M	10	F	2	4	2	9	12	TO	No	data	196	No	+
J	28	M	10	F	4	..	3	14	..	None	1	V	133	No	±
K	26	M	18	F	4	4	39 ⁸	120	6	TO, I↓	2	HNS	237	Yes	±
L	27	M	31	F	4	0	14	45	5	TO	..	None	110	Yes	0
M	34	M	39	F	2	2	17	51	2	T↓	..	None	150	Yes	0
N	29	F	24	D	4	0	10	31	3	I↓	1	MS	325	Yes	0
O	24	F	40	D	2	0	42	102	3	TO	5	VW	107	Yes	0
P	19	M	42	D	4	0	20	80	5	TO	14	M	20	Yes	—
Q	17	M	47	D	4	0	7	27	2	I↓	..	None	10	No	—
R	31	M	53	D	4	0	19	85	7	T↓	2	HS	39	No	—
S	24	M	70	D	4	0	11	39	4	T↓	1	H.A.	11	Yes	—
T	21	M	72	D	4	0	2	9	4	T↓	1	HV	298	No	±
									2	T↓	2	ASV		Yes	—
									2	T↓	2	F.E.		No	±

¹ NF = non-fluctuant; F = fluctuant; D = draining.² 4 = positive; 2 = doubtful.³ T = tenderness; I = induration; F = fever; ↓ = diminished; 0 = absent.⁴ A = anorexia; D = dyspnea; H = headache; M = mental clouding; N = nausea; P = palpitation; S = sleepiness; V = vertigo; W = weakness; H.A. = hemolytic anemia; F.E. = fixed eruption.⁵ + = persistent inflammatory activity; ± = persistent asymptomatic residua of past inflammation; 0 = negative findings; — = not followed long enough for final examination.⁶ No residua of adenitis, Waelsch urethritis.⁷ See text. Patient received 42 gm. of sulfanilamide in 12 days with good clinical response. Twenty-eight days later, after relapse, treatment was resumed and 48 gm. were taken in 14 days.⁸ See text. Patient received 105 gm. of sulfanilamide in 34 days, with good clinical response. Fourteen days later, after relapse, treatment was resumed and 15 gm. were taken in 5 days.

Chart 1 presents the composite picture of the chemical changes by weeks in the 16 patients who had more than one plasma protein determination in the 7 weeks following institution of sulfanilamide therapy. It may be seen that before treatment, total protein and

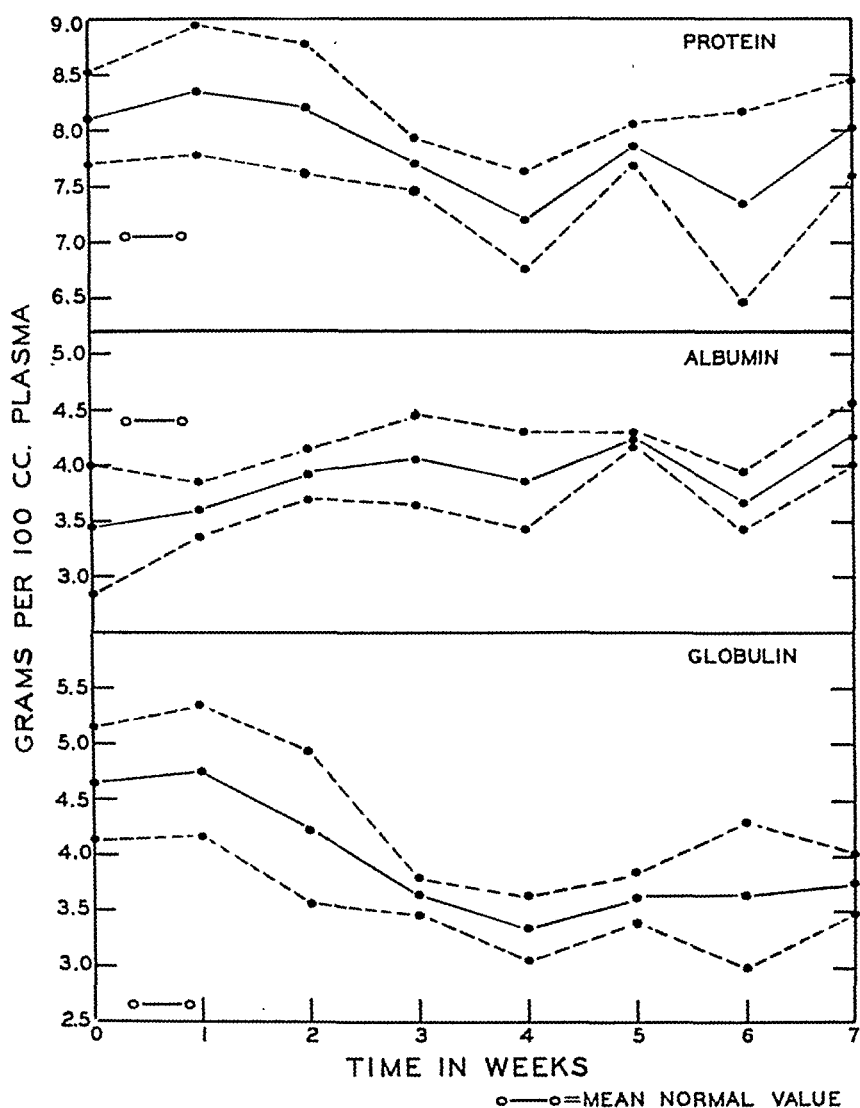


CHART 1.—Means and standard deviations of plasma protein in the 16 patients who had two or more determinations within 7 weeks after beginning sulfanilamide treatment. Determinations made 0 through 3 days after start of treatment were charted as 0 weeks, 4 through 10 days as 1 week, 11 through 17 days as 2 weeks, and so on. Mean normal value is that determined by Peters and Van Slyke.¹⁵

globulin values were higher than normal, and the albumin values lower. Clinical improvement under sulfanilamide treatment was paralleled by a trend toward normal in the chemical picture, which was most marked in the globulin.

Chart 2 demonstrates the striking reversal of the albumin-globulin ratio before treatment was started, and the more nearly normal values after treatment in the same patients. Only 1 patient of 18 presented a ratio greater than 1 before treatment, but in the final determination, 12 of the cases had ratios greater than 1, and a number of these approximated the normal value.

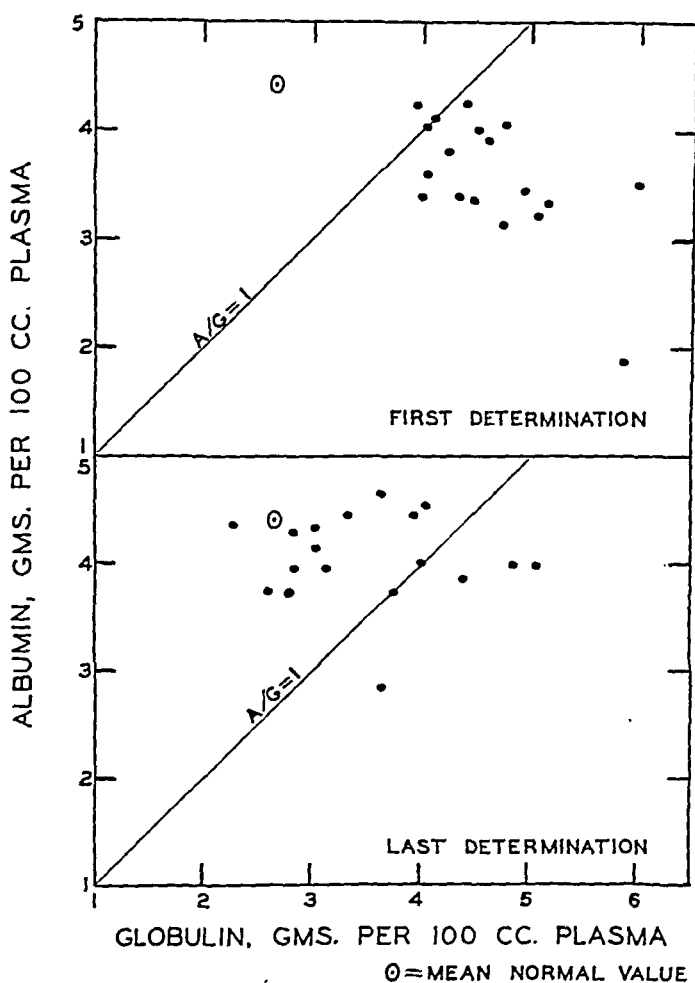


CHART 2.—First and last determinations of albumin and globulin in 18 patients. Final determinations were made 7 to 302 days after the start of sulfanilamide treatment. Circled point indicates mean normal value for comparison (Peters and Van Slyke¹⁵).

In Chart 3, the 15 patients who were observed clinically and chemically 102 to 302 days after beginning treatment were separated into two groups. Eight cases showed absolutely no objective residua of lymphadenitis and were considered "cured." All of these patients had responded rapidly to sulfanilamide treatment. Of the 7 patients classified as not completely cured, 3 had originally

responded well to treatment, and 4 had been considered treatment failures. Not one had subjective complaints (tenderness or discomfort) referable to his inguinal lymph nodes. The differentiation was made on the basis of firm, almond-sized, discrete inguinal nodes in 3 patients (A, H, and J), mild residual thickening of the overlying

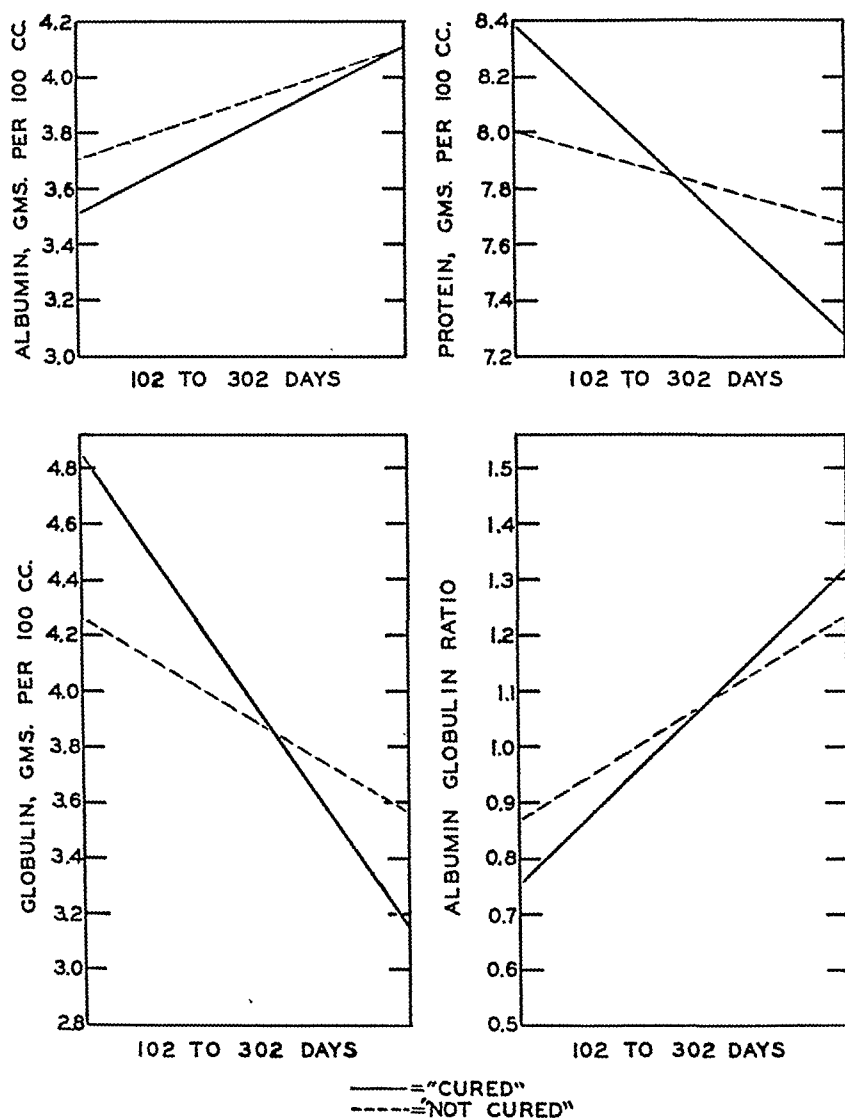


CHART 3.—Mean initial and final plasma protein determinations in the 8 "cured" and 7 "not cured" patients who were followed for 102 to 302 days after the start of sulfanilamide treatment. Initial values were further from normal, final values nearer normal, in the "cured" group.

skin in 2 (K and T), adherent matted nodes in 1 (I), and a persistent mild urethral discharge in Case G, which may have been a Waelsch urethritis caused by the virus of lymphopathia venereum. Chart 3 demonstrates that the patients who were clinically cured presented

on admission a more marked chemical aberration from normal than did the "uncured" patients, and on follow-up examination, were closer to the chemical norm. The mean duration of adenitis when the patient was brought under treatment was essentially the same in the two groups.

Appendix A lists all of the plasma protein studies made in all 20 patients.

Discussion. Inguinal adenitis caused by the filterable virus of lymphopathia venereum is known to vary greatly in the severity and duration of its manifestations. In some patients, very mild enlargement and tenderness of the lymph nodes subside quickly without suppuration, while in others, the disease is severe, characterized by fever, prostration, and persistent suppuration of the lymph nodes for a number of months. Evaluation of a therapeutic agent directed at so variable a disease entity is fraught with difficulties, for the investigator must attempt to differentiate between spontaneous and therapeutic improvement.

Our patients were closely observed at frequent intervals, and we feel that certain phenomena seen indicate that sulfanilamide radically influenced the course of the disease. The dramatic disappearance of fever and malaise in the 2 patients who had constitutional symptoms on admission, the rapid relief of pain and tenderness in the involved lymph nodes in 14 patients, and the relapse of 2 patients 7 and 21 days after withdrawal of the drug, strongly suggest that improvement under treatment was more than coincidental.

All of our patients presented at the beginning of treatment a high plasma globulin value which fell parallel to clinical improvement while under treatment and in the months following, so that there was an approximately normal value in one-half of the patients at the end of the observation period. Rosen¹⁶ has shown that patients with latent lymphopathia venereum, characterized only by a positive Frei test, maintain a persistent hyperglobulinemia for many years after infection. It is, therefore, pertinent to speculate why half of our patients, only 3 to 10 months after infection, had no remaining chemical abnormalities.

Stein²⁰ has recently reported reversal of the Frei test from positive to negative in 4 of 5 patients retested 6 to 8 months after sulfanilamide treatment of inguinal adenitis due to lymphopathia venereum. The specific skin sensitization to dead lymphopathia virus, which may be demonstrated years after infection in untreated patients, appears to have been quickly lost by these cases after effective early treatment. These findings may be based upon the same mechanism as the return toward normal of the plasma globulin in our cases.

Hyperglobulinemia of greater or less extent occurs in most infectious diseases, and the hyperproteinemia and hypoalbuminemia are considered secondary to the globulin increase. Specific humoral antibodies to infectious agents are associated with the globulin

APPENDIX A.

PLASMA PROTEIN CHANGES IN 20 NEGROES WITH EARLY LYMPHOPATHIA VENEREUM PRESENTING INGUINAL ADENITIS, UNDER TREATMENT WITH SULFANILAMIDE.

(Plasma Protein, Grams Per 100 cc.)

Case.	Duration of adenitis before treatment (days).	Days after start of treatment.	Total protein.	Albumin.	Globulin.	Albumin- globulin ratio.
K	18	0	7.59	3.57	4.02	0.89
		11	7.54	4.22	3.32	1.27
		20	7.46	3.66	3.80	0.96
		34	7.70	4.31	3.39	1.27
		41	6.34	3.55	2.79	1.27
		48	8.26	4.63	3.63	1.27
		69	8.20	4.26	3.94	1.08
		118	7.29	3.86	3.43	1.13
		237	7.16	4.15	3.01	1.38
E	17	0	8.07	4.03	4.03	1.00
		3	7.57	3.71	3.86	0.96
		7	7.91	3.72	4.19	0.89
		14	8.10	4.13	3.97	1.04
		28	6.97	4.11	2.86	1.44
		42	6.64	3.32	3.32	1.00
		56	6.88	4.06	2.82	1.44
		164	6.84	3.97	2.87	1.38
H	28	0	8.48	3.99	4.49	0.89
		33	8.07	4.20	3.87	1.08
		40	8.11	3.97	4.14	0.96
		49	8.44	4.14	4.30	0.96
		75	8.50	4.50	4.00	1.13
		105	7.79	3.97	3.82	1.04
		233	8.47	4.49	3.98	1.13
B	11	4	8.49	3.91	4.58	0.85
		10	8.38	4.11	4.27	0.96
		17	7.80	4.06	3.74	1.08
		23	7.92	4.44	3.48	1.27
		30	7.91	4.27	3.64	1.17
		147	7.16	4.29	2.87	1.50
M	39	0	8.41	3.45	4.96	0.70
		10	8.28	3.48	4.80	0.72
		47	7.40	4.00	3.40	0.85
		150	7.11	3.98	3.13	1.27
D	14	0	8.49	3.31	5.18	0.64
		28	7.25	3.94	3.31	1.13
		56	7.13	—	—	—
		302	8.28	4.64	3.64	1.27
N	24	0	9.34	3.11	6.22	0.52
		17	8.48	3.05	5.43	0.56
		325	8.51	3.40	5.11	0.67
T	72	0	7.42	3.42	4.00	0.85
		61	8.02	4.01	4.01	1.00
		298	6.64	4.38	2.26	1.94
G	28	0	7.75	3.41	4.34	0.79
		25	6.66	3.13	3.53	0.89
		279	6.48	2.85	3.63	0.79
C	14	0	7.73	1.86	5.87	0.32
		7	7.65	3.37	4.28	0.79
		212	6.35	3.75	2.60	1.44
J	10	0	8.65	4.24	4.41	0.96
		12	8.59	3.87	4.72	0.82
		133	8.60	4.56	4.04	1.13
A	4	0	7.84	3.37	4.47	0.75
		7	7.88	3.31	4.57	0.72
		123	9.07	3.99	5.08	0.79
O	40	9	9.51	3.52	5.99	0.59
		14	9.49	3.80	5.69	0.67
		107	8.03	4.01	4.01	1.00
R	53	0	8.29	3.23	5.06	0.64
		12	8.25	3.38	4.87	0.70
		39	8.24	3.87	4.37	0.89
I	10	0	8.21	4.10	4.10	1.00
		206	7.37	4.35	3.02	1.44
L	31	12	8.19	4.26	3.93	1.08
		110	6.51	3.71	2.80	1.32
F	17	0	8.07	3.74	4.28	0.89
		102	7.80	4.44	3.36	1.32
S	70	0	7.88	3.15	4.73	0.67
		11	7.50	3.75	3.75	1.00
P	42	0	8.79	4.04	4.75	0.85
		7	8.87	3.99	4.88	0.82
Q	47	0	8.40	—	—	—
		7	8.42	5.39	3.03	1.78

fraction of the blood proteins, and, *in lieu* of evidence to the contrary, it appears reasonable to assume that increase in globulin in infectious diseases results from the elaboration of humoral antibodies. If this premise is correct, we find antibody formation in early lymphopathia venereum, and its persistence for years in untreated patients, but loss of humoral antibody in patients cured early in the course of their infection.

Eagle^{3a} believes that reagin, the substance in syphilitic serum responsible for the production of positive serologic tests for syphilis, is a true circulating antibody against the *Treponema pallidum*. It is well known^{3b} that the majority of syphilitics treated energetically early in the course of their infection, with arsenical and bismuth compounds which are specific against *T. pallidum*, achieve persistent seronegativity, whereas untreated patients, and patients first treated late in the course of the disease, maintain, in most instances, a positive serologic test for syphilis. It is also established⁷ that only patients treated early in their syphilitic infection are susceptible to reinfection. As an explanation of these observed phenomena, it has been suggested that immunity against syphilis develops early in the course of the disease, and, unless interrupted relatively early by treatment, persists throughout the life of the individual and is demonstrable years later by a positive serologic test and resistance to reinfection.

It is suggested, on the basis of the serochemical findings in this paper, that an analogous situation occurs in lymphopathia venereum. Hyperglobulinemia may be considered an indicator of the presence of humoral antibodies and hence of immunity, even as reagin is so considered in syphilis. Thus, a high initial globulin level in a patient with lymphopathia venereum might indicate a strong antibody response to the infection, and hence spell a good prognosis, and a low final globulin value which approaches normal, after specific treatment, might suggest complete destruction of the virus and cure. The higher initial blood globulin level in our group of "cured" patients, and the lower final value, as presented in Chart 3, is in accord with this hypothesis.

Untreated, the patient with lymphopathia venereum maintains a hyperglobulinemia for many years, as has been shown by Rosen. When treated early with sulfanilamide, the abnormal serochemical values tend to return to normal. It is suggested that this may represent an early inhibition of antibody formation, due to complete destruction of antigen by a potent therapeutic agent. It is further suggested that a high initial globulin is of good prognostic import, and that return to normal of the blood globulin is an indicator of adequacy of treatment in early lymphopathia venereum.

Summary and Conclusions. 1. Serochemical and clinical observations were made on 20 negroes presenting inguinal adenitis due to lymphopathia venereum, under treatment with sulfanilamide.

2. Fourteen (70%) of the patients experienced rapid relief from their symptoms as a result of treatment, although objective improvement was slower. One hundred and two to 325 days after institution of treatment, 9 of the 16 patients reexamined (56%) were free of any evidence of disease, and 7 (44%) still showed asymptomatic residua.

3. All of the patients presented an initial hyperglobulinemia, which reverted toward the normal level as clinical improvement was manifested.

4. It is suggested that the increase in blood globulin uniformly seen represents a humoral antibody response against the virus of lymphopathia venereum, and that its reduction to normal in patients treated early with sulfanilamide demonstrates inhibition of antibody formation through destruction of the virus.

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THE EFFECT OF SMOKING TOBACCO ON GASTRIC ACIDITY.

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THE effect of tobacco smoking on gastric function in its various aspects has become a subject of considerable literature. There is a wide clinical impression that smoking causes, aids in causing, aggravates, or prevents healing of peptic ulcer.^{1,5,9,10,16,25} This doubtless

is responsible for much of the speculation as to what tobacco smoking does to the stomach and what it is in the smoking that does it. It has been extensively stated that smoking increases gastric acidity.^{7,12,17,22} There is evidence that gastric motility is affected.^{6,23} It has seemed to some^{4,8,14,15,18,26} that nicotine produces these effects from its action on the autonomic nervous system.¹¹ Thus Arthur

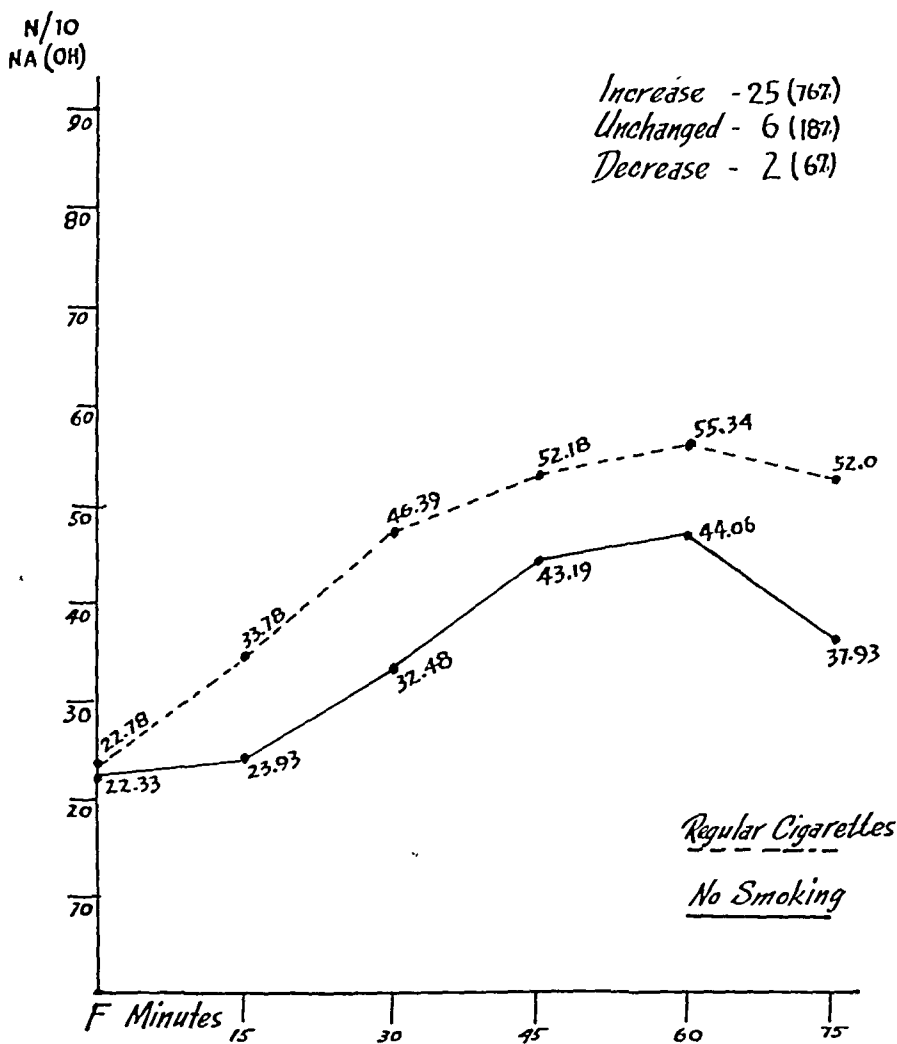


CHART 1.—Control group (33 cases).

Hurst⁹ holds that, since the parasympathetic is in the ascendency in ulcer subjects, that system is more responsive to nicotine. There is some evidence also of the toxicity of tobacco tar.³ The entire subject has been a matter of controversy and opposing views expressed according to the various approaches of the discussants. For example, Hurst⁹ finds that a large proportion of patients that

have duodenal ulcers have smoked excessively for years while Barnett² and Trowell²⁴ each found the per cent of smokers in an ulcer group about the same as for a control group. Hurst thinks that inhaling the smoke is not a factor and Trowell thinks that inhalation may be a big factor. Schnedorf and Ivy²¹ have pointed out the fact that present-day concepts are based on clinical and personal experience and that few experimental data exist on which to base an explanation of clinical observations.

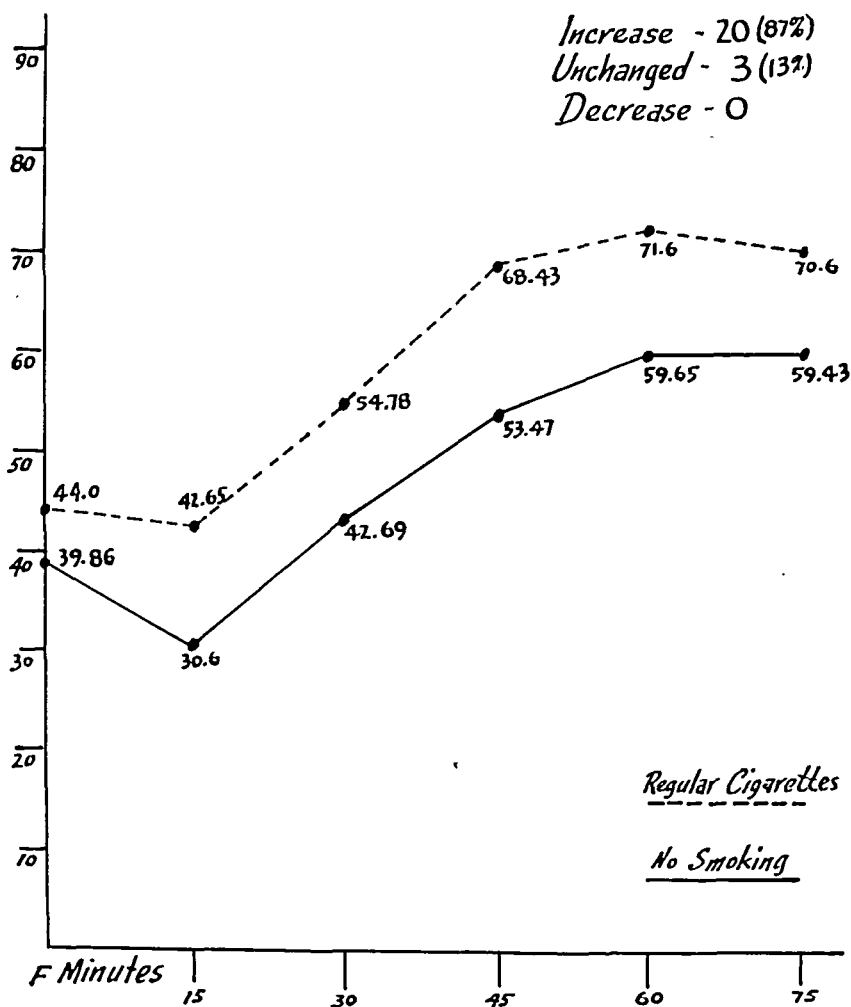


CHART 2 — Ulcer group (23 cases).

Sacchetto and Testolin²⁰ found an increase in gastric acidity after smoking. Gray⁷ reported a hypersecretion in 50 of 63 ulcer patients following the use of tobacco and an increase in acidity in one-quarter of these cases, 3 showing a decrease. Mall and Flint¹³ found that daily injections of nicotine in humans over a period of 2 to 3 weeks markedly increased gastric acidity in 5 of 6 patients. Rosenblum

found a significant increase in free and total hydrochloric acid after cigarette smoking with the patient fasting. Schnedorf and Ivy²¹ studied the effect of smoking 4 to 7 cigarettes on the fasting secretion of 25 smokers, 15 non-smokers and 20 patients with duodenal ulcer. In only 1 of the 40 normal subjects were the volume and acidity of the fasting secretion augmented. In 22 an appreciable

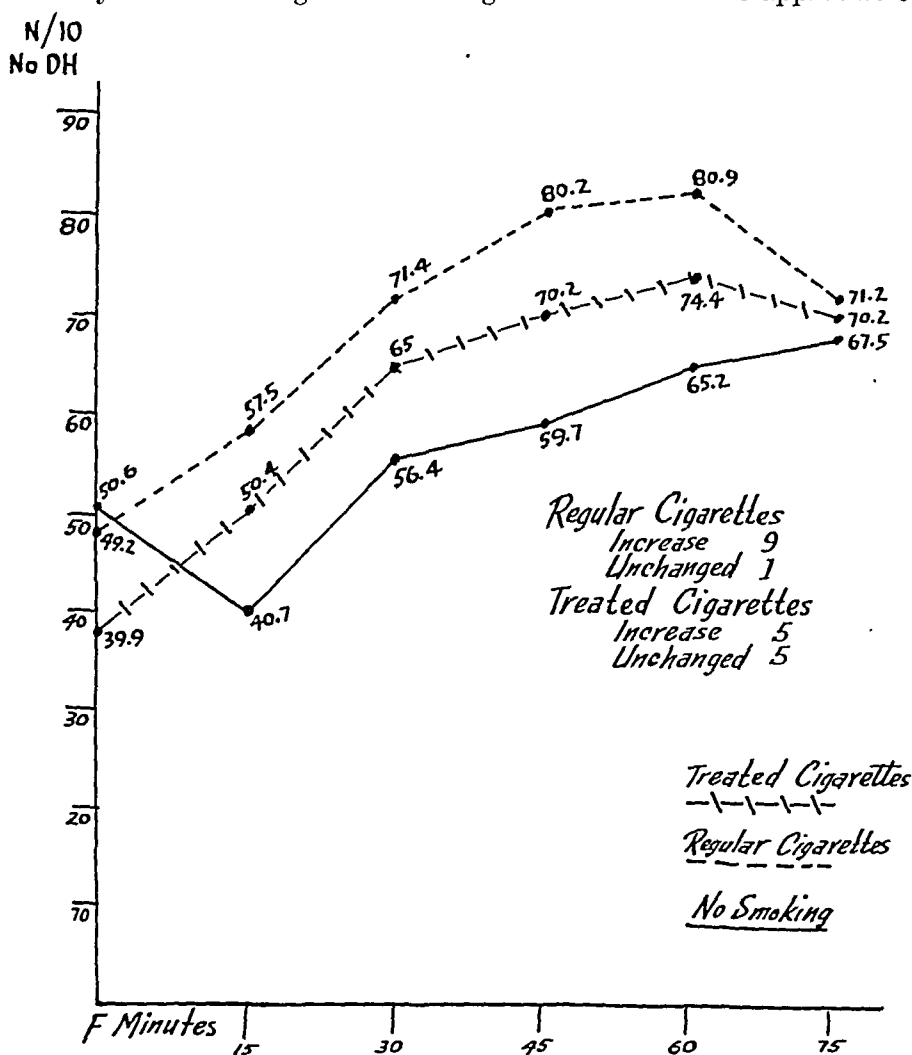


CHART 3.—Total acidity values (10 cases).

decrease in both volume and acidity resulted. In only 1 of the 20 patients with ulcer did any significant increase in gastric acidity take place, while there was a decrease in 11. Using denicotinized cigarettes there was some depression of the gastric secretion. Similar results were obtained by smoking after taking a test meal. These findings are somewhat at variance with those obtained by the authors with a similar approach.

Method. Fractional analyses were made on patients on successive mornings after a fasting period of 12 hours. One morning the analyses were made without smoking, one morning following the smoking of 2 cigarettes. On each of the two mornings the fasting juice was removed and the patient given 200 mls of 7% alcohol. Specimens were then taken every 15 minutes for 1 hour and 15 minutes or longer. The samples were tested immediately upon removal by titrations with $\frac{N}{10}$ sodium hydrate solution, using dimethylamidoazobenzol and phenolphthalein as indicators. In each group tested approximately one-half the number smoked the first day and the remainder smoked the second day. This was done to neutralize any effect that emotional adjustment to the passage of the tube might have on the acidity values.

Results. 1. A control group of 33 patients without gastro-intestinal lesions were studied. Twenty-five (76%) showed definite increase in gastric acidity after smoking over the values obtained when not smoking. Six (18%) showed no change while 2 (6%) showed a slight decrease (Table 1, Chart 1).

2. Of the 23 patients with peptic ulcer, 20 (87%) showed a definite increase in both free hydrochloric acid and total acidity in the gastric analyses done following the smoking of 2 cigarettes. Three showed no change from normal (Table 2, Chart 2).

3. Ten patients were given gastric analyses on 3 successive days, 1 without smoking, 1 after smoking 2 of the popular brand cigarettes and the third after smoking partially denicotinized cigarettes (nicotine 0.74%). Nine (90%) showed definite increase in acid values after smoking popular brand cigarettes, whereas, after smoking partially denicotinized cigarettes, 5 showed no change and 5 showed very slight increase in acid values (Table 3, Chart 3).

Discussion. Definite increase in gastric acidity after smoking 2 cigarettes has been obtained in a significant group of controls and patients with peptic ulcer. The increase seems to be associated with the presence of nicotine, though there could be no assurance that the removal of the nicotine did not also remove other substances.

Patients were not asked to expectorate their saliva. This leaves the effect of the reaction of the saliva unexplained. In our experiment 2 cigarettes were used. In the tests performed by Schnedorf and Ivy, 4 to 7 cigarettes were smoked in periods up to 80 minutes. There is reason to suspect that the amount of smoking would vary the result, in that limitation to a certain amount may give stimulation of secretion and motility followed by inhibition but that with more smoking the initial period may be shortened or even disappear. The amount of alcohol was the same in each test and possible synergistic action of alcohol and smoking has not been ruled out.

Conclusions. Significant increase in gastric acidity follows smoking under certain test conditions. This is slightly greater in a group of patients with peptic ulcer than in a control group. It seems to be more marked in smoking untreated cigarettes than after smoking cigarettes from which part of the nicotine had been removed.

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ASSOCIATION OF THE INTERNIST AND PSYCHIATRIST IN PRIVATE PRACTICE.*

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THE increasing interest of the medical specialties in one another and in their common problems is a trend of recent times, particularly in the fields of internal medicine and psychiatry. Consequently, it would be well for organizations of internists and psychiatrists to discuss the advantages of and the obstacles to closer coördination, especially in the realm of private practice. Through our association in private practice as internist and psychiatrist, we feel that we have solved many of the problems common to both specialties and that we have enjoyed many advantages. With the initiation of definite methods of approach and referral, we feel the result has been that the individual patient is more readily and adequately treated as a psychobiologic unit.⁴

The internist in private practice is often confronted with chronic illnesses. He frequently finds involved personality factors which, in most instances, are of sufficient importance to warrant serious

* Read at the meeting of the American Psychiatric Association in Chicago in May, 1939.

consideration in both diagnosis and therapy. Many such cases are entirely personality-determined or functional, and others present admixtures of organic and psychiatric features and etiologies.

The psychiatrist without association in private practice is rarely in a position to contact early cases of maladjustment. He necessarily is dependent on referral from his contemporaries. Early maladjustments most commonly call upon physicians other than psychiatrists and early referral is dependent on the physician's attitude and approach. If early psychiatric treatment can be established, it should be evident that more satisfactory results will be obtained and many serious disorders averted. Chronicity and fixation of reaction will in many an instance be forestalled. A decade ago the psychiatrist was concerned almost entirely with the major psychotic reactions, but in recent years his attention has shifted not only to the minor reactions of neurotic and toxic-organic types, but to complicating personality maladjustments associated with physical illnesses. A fertile field of psychotherapy should lie then in close association with the internist. On the other hand, the physical disorders encountered by the psychiatrist often need a consultant's care unless they be of very minor importance. Frequently the rôle of organic factors may be difficult to evaluate by the psychiatrist without consulting assistance. Haphazard referral, however, to medical consultants lacking fundamental knowledge of psychiatry may lead to complicating misstatements, psychologic bungling, and unnecessary diagnostic procedures with a deleterious effect.

In view of these problems an internist and psychiatrist may find the solution in a close association, as we have. The combination leads to a better psychobiologic approach in private practice to the patient's complaints, a situation comparable to the demonstrated value in clinics, hospitals, and medical centers.

The *modus operandi* of the association must vary according to the individual patient. The internist studies him in the customary manner through history, physical examination, and laboratory tests limited to fluoroscopy, hematology, urinalysis, and Wassermann. The patient is then given an appointment to return in 48 hours, allowing time for preliminary formulation. Should a psychiatric problem or complication be detected, the internist formulates the findings to his associate psychiatrist and together further procedure is decided upon. The question of further clinical and laboratory studies is discussed and decisions carefully reached, because such procedures as those involving the electrocardiograph, basal metabolic apparatus, Roentgen ray equipment, and others, may be unnecessary, add to expense, and help concentrate the patient's attention upon his body. In rare instances extensive studies may be indicated in order to help reassure the patient as to his physical status. The conjoined opinion of the internist and the psychiatrist

may be to postpone referral to the psychiatrist if the problem is simple; if the physical factor is of major significance and the personality deviation minor; if there is great personal resistance to psychiatry on the part of the patient; or if the dependence of the patient on the internist is, at the time, too great to warrant abrupt change. Whatever the course may be, the rôle of the psychiatrist is prominent in diagnosis and therapy. The attitude and technique of the internist will almost always bring the patient to referral if the psychiatric problem is important. In the process of referral the internist gives his patient a preliminary formulation of personality dysfunction or complication in a common-sense lay language. He may explain the relationship of tension and emotion states to abnormal organ functioning. He may cite common every-day instances of accidents, grief, anger, and the like, and their emotional counterpart in the development of symptoms and distress. With certain intelligent patients he may adopt a more specific psychobiologic approach. Other patients, less intelligent or less well equipped to digest explanation, may be told that their trouble is due to "nerves" and that they should be seen by a specialist. A few are informed that an office associate is particularly interested in their type of case and that he should be called in. In all instances it is definitely easier to get the patient to consent to referral to the psychiatrist as an office associate, conveniently at hand. In order to avoid patient-physician fixation and thus make referral difficult, the internist intentionally avoids too deep aëration of the patient's personal problems. The first physician to hear the detailed story is in a better position to administer therapy. Consequently, intensive aëration is left to the psychiatrist.

The internist should continue with an active interest in the patient after referral to the associate psychiatrist. In strictly psychiatric or physical conditions, decisions and responsibilities rest primarily with the appropriate specialist, while psychosomatic admixtures require a sharing of judgment and responsibilities of the two. Frequent criss-cross consultations between the two physicians will be informative, instructive, and educational to both. Etiologies, psychodynamics, physiology, interrelationships of somatic factors, therapeutic plans, and results are discussed at frequent intervals. In other words, through the association of the internist and psychiatrist the patient is studied and treated as an individual unit. A process of joint postgraduate education is in operation in each instance for both internist and psychiatrist, and a more common ground of understanding and coöperation is established.

The psychoneurotic reactions are the most common psychiatric conditions met in private practice. Simple and early cases may be managed for the most part by the internist, but when possible the associate psychiatrist should handle the therapy of these individuals. The following illustrate commonplace psychoneurotic problems encountered in practice.

A 27-year-old, single housemaid consulted with the internist for complaint of right-sided headache. There was a history of skull fracture 15 years ago. The patient blamed headache on the head injury and later on, goiter. Physical and neurologic examinations were negative. The basal metabolic rate was normal. Referral to a psychiatrist revealed well-concealed hysteria of long duration, and life-long feelings of insecurity, masturbation conflict, employment problem, and negligible outlets. The complaints readily subsided with psychotherapy.

A middle-aged, married woman with a tubercular husband practised nursing until 8 years ago when her family physician advised rest for complaints of fatigue. She had a rapid pulse and persistent afternoon fever. The patient remained inactive with continued complaints for the subsequent 7 years. A diagnosis of pulmonary tuberculosis was suspected but never confirmed. The patient received compensation insurance. Frequent examinations, consultations, and trips to large clinics with continual warnings to rest resulted in a chronic invalid pattern. She was finally referred to a psychiatrist over her husband's objections. Complete examination revealed a health-conscious individual with hypochondriasis. A formulation of her problem with an activity program led to satisfactory adjustment.

Depressive reactions in private practice are probably quite common, although incipient cases are missed frequently. In recent years psychiatrists have recounted the frequency of biologic complaints² which send the depressed patient to his family physician. As a rule, the psychiatrist is called in at a late date.

A 23-year-old housewife was seen by an internist 2 months after the uneventful delivery of a normal baby. Complaints were insomnia (early morning waking), anorexia, general malaise, loss of pep, poor concentration, and a feeling of being "down in the dumps." Psychiatric study revealed fixed ideas of self-incrimination, retarded motion and thought, and definite suicidal preoccupations. The case was formulated as a retarded depression to the patient's relatives, who at first refused to accept anything but an organic diagnosis, while the husband contended his wife was malingering. Hospitalization with a stimulating activity program, conservative psychotherapy, and close follow-up led to a recovery and ultimate better understanding by relatives and husband.

Patients ailing from psychosomatic admixtures constitute a relatively large group in private practice. The ready availability of both internist and psychiatrist affords a satisfactory and efficient solution to most of these conditions. Criss-cross consulting and sharing of responsibility results in a more total therapy for the individual patient.

Radical forms of treatment emanating from either specialty may be modified or contraindicated after complete study by the asso-

ciated internist and psychiatrist. This is particularly applicable to shock therapy, and many times to contemplated surgery.

A 50-year-old single woman suffered from an autogenous depression. Treatment by conservative means over a period of months was ineffective. The psychiatrist desired to administer shock therapy but hesitated because of a history of active pulmonary tuberculosis 10 years ago. After careful general and cardiopulmonary study the internist concluded there was no active pulmonary tuberculosis or other contraindication. Metrazol shock therapy assisted in restoring the patient to a satisfactory adjustment.

A married salesman, 50 years of age, suffered from pulmonary tuberculosis with cavitation. Pneumothorax attempts failed. A thoracoplasty was performed and in the postoperative convalescence the patient developed a serious delirious reaction with depressive content. Psychiatric consultation was called after the reaction was well developed and ultimate care for both the psychiatric and somatic conditions was prolonged and trying. Early psychiatric consultation prior to thoracoplasty would probably have advised against operative procedure and recommended a more conservative therapy. There was a history of previous depression in recent years, and the patient had been fearful and apprehensive over an operative procedure in the past.

The psychiatrist using shock therapy is in need of an internist's opinion and advice on many occasions. The internist should help select candidates for shock therapy through careful cardiovascular renal studies, and in the event of complications he should be readily available.

Psychiatric and somatic conditions may be found existing concurrently or may arise as complications of one or the other. Chronic alcoholism often presents problems common to this group. The delirious and confusional states of cardiovascular disease, particularly cerebral arteriosclerosis and hypertension, are frequent. Depressed reactions and anxiety states present in combination with serious underlying physical maladies often occur in chronic arthritis, asthma, syphilis, coronary disease, and brucellosis. The latter condition, brucellosis, is apt to show many complaints and symptoms common to the psychoneuroses and depressions: general malaise, easy fatigability, insomnia, anorexia, impaired concentration, emotional instability, fugitive aches and pains, and paresthesias.

A 36-year-old, single man was given vaccine therapy for a definite chronic brucellosis. Complaints of fatigue and indigestion failed to respond to the vaccine treatment. After offering some resistance, the patient was referred to the psychiatrist who found an obsessional-compulsive psychoneurosis with hypochondriacal features. Psychotherapy in combination with brucella vaccine is giving a more satisfactory result.

There is one definite problem which faces the association of internist and psychiatrist in private practice and that is the compartment-

ship which still exists between the two specialties. Referral of patient from the internist is in many instances a difficult task. The cause may be laid at the doors of the internist, the patient, and the psychiatrist.

The internist contributes to the difficulty of referral because of his approach to the patient. Formerly as a student he was taught and trained to consider patients primarily from an organic standpoint and the diagnosis of psychiatric disorders was made by exclusion. In general he deals with disease entities rather than with personalities and individuals. With this approach physical examination and laboratory studies are exhausted in an effort to find some organic physical explanation for the symptomatology. Treatment ends with complete dismissal, or the patient is carried along indefinitely in a symptomatic manner with sedatives, tonics, diet, vaccines, and so on. Surgical procedures not infrequently are resorted to in an effort to relieve the patient's symptoms. If the patient is suffering from a functional disorder and is treated symptomatically, the psychiatric condition remains fixed, the progress of the maladjustment is encouraged, and attention to the patient's body and health are reemphasized. With progress of the functional disorder the internist becomes more baffled. Either the patient or the internist gives up and the patient shifts to another physician, or perhaps resorts to osteopathy, chiropractic, or Christian Science. If, after his failure, the internist realizes that psychiatric consultation and treatment are necessary, the patient is in no position for referral. One can readily see that an organic approach, devoid of personality understanding, encourages fixation of the functional disorder and makes psychiatric treatment impossible.

The attitude of the patient, apart from that due to previous medical experiences, may be the existing reason for difficult referral to a psychiatrist. Due to folklore and medieval thought many patients feel that it is a disgrace or a family reflection to consult a psychiatrist. It is true this archaic attitude of the public is subsiding, but in many places it remains unchanged. The psychiatrist or his patient still appears in an unfavorable light in court trials, movies, novels, and cartoons. The neurotic continues to be the butt of jokes and by the uninformed is thought of as a malingerer. From the patient's standpoint the chief obstacle to psychiatric referral is prejudice, due to social inheritance, ignorance, and fear.

The psychiatrist plays a rôle in the problem of referral. Historically he, in the mind of the public, has been associated largely with treatment of major psychoses in institutions. His research, until recent years, has largely been carried on independent of other branches of medicine. His terminology and concepts are frequently beyond the understanding of the average practitioner. Until recently his only close association with other specialties has been in institutions, medical schools and large clinics. It is true that almost every community has its quota of competent psychiatrists engaged

in private practice, but we believe that they fail to be introduced to most of the individuals needing their services.

Advances have been made over the past few years which undoubtedly are rendering the public more psychiatric-minded. Psychiatry must be made more available to the public through the general practitioner, internist, pediatrician, gynecologist, and surgeon. The improved status of psychiatry in medical schools^{3b,c,d} is, of course, a major advance in this direction. The introduction of a psychiatric service into the general rotating internship^{1c} is being rapidly accomplished. The establishment of psychiatric liaison departments^{1a,b,3e} in large general hospitals and of refresher postgraduate courses represents a step to reach the older men in medicine who lacked the opportunity of early psychiatric training. The fellowship psychiatric training program^{3a,e} is rapidly turning out well-equipped psychiatrists who may help in the education of their fellow professional contemporaries. The establishment of the American Board of Psychiatry and Neurology is an indication of psychiatry's high standards.

If psychiatry and internal medicine can continue toward the common ground of mutual interest and endeavor, a more comprehensive service will be rendered to the public. We feel that a closer association of the internist and of the psychiatrist in private practice is a means to this end.

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ROENTGEN THERAPY OF EXPERIMENTAL LOBAR PNEUMONIA IN DOGS.*

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FOR the past 3 years we have been studying the effects of Roentgen therapy on experimentally produced lobar pneumonia in dogs.

* Financed by a grant from the Research Fund of the Class of 1908 of the Medical School of the University of Pennsylvania.

While this work was in progress, the use of sulfapyridine and its related chemical compounds and the wider availability and greater potency of specific antipneumococcic sera resulted in a striking reduction in the mortality of lobar pneumonia. Because these types of therapy were so successful, it might reasonably be concluded that research directed toward other forms of treatment of this disease would prove to be of more academic than practical value. Nevertheless, we were encouraged to pursue our investigations because of enthusiastic clinical reports in the literature which claimed that Roentgen therapy of lobar pneumonia had reduced the mortality of this disease to that figure which had been achieved by specific chemotherapy and serum.

The enthusiasm which has been evinced in certain quarters for the Roentgen therapy of lobar pneumonia has had little background of animal investigation. This is entirely comparable to the state of affairs which existed a few years ago when unrestrained use of therapeutic pneumothorax in this disease preceded, instead of followed, experimental research on animals.⁶

We therefore undertook a study of the effects of Roentgen therapy in experimentally produced lobar pneumonia in dogs. For this purpose, 45 animals were infected; of these 26 were treated and 19 permitted to serve as controls. Roentgenograms or fluoroscopic examinations were used to confirm the presence of pulmonary disease and delineate it.

Historical. In 1907, Edsall and Pemberton² reported beneficial results from Roentgen therapy for delayed resolution of lobar pneumonia. In 1916, the Quimbys⁹ reported 12 cases of delayed resolution improved by irradiation and expressed the opinion that this treatment should be used if resolution was delayed 5 days after its predicted onset. They stated that this treatment was effective when instituted as long as 3 months after the expected crisis.

The first real progress in the study of Roentgen therapy in pneumonia was made in 1924 when Heidenhain and Fried^{4a,b} reported the use of irradiation in pneumonia and in subacute suppurative processes. Their results in the treatment of various infections with Roentgen therapy were not uniform but they were particularly impressed with its effect in pneumonia. At that time these investigators irradiated only those cases in which no improvement followed the customary methods of treatment. In the light of more recent knowledge, we suspect that their technique was inadequate. In 1926, Fried^{3a} reported the results which he obtained with Roentgen therapy in 40 cases of postoperative pneumonia. It is probable that some of these cases were instances of postoperative pulmonary atelectasis. He classified his results as very good in 20 cases, good in 12, doubtful in 1, and negative in 7. A subsequent report^{3b} in 1928 claimed essentially the same results. In this country the publications of E. V. Powell have continued to excite interest in many clinics. In 1936^{8a} he reported his experiences in the Roent-

gen treatment of 47 cases of untyped lobar pneumonia. The first technique which he employed was that commonly used in the treatment of carbuncles and other infections. His results in pneumonia were strikingly good, the mortality being 2.5%. Subsequently, in 1938,^{8b} in 57 cases of lobar pneumonia more adequately studied, the mortality rate was essentially the same. In the latter series the technique differed somewhat from that used in the original cases. In his most recent contribution Powell^{8c} reports 105 cases of lobar pneumonia with 5 deaths, and 30 cases of bronchopneumonia with 4 deaths. In an additional note in this publication Powell states under date of February 14, 1939, that he has treated a total of 231 patients with pneumonia by irradiation with 16 deaths, a mortality of 7%. He does not specify respectively the number of patients with bronchopneumonia and lobar pneumonia. He makes the astounding statement that all of his patients with Type II and Type III pneumonia, respectively, treated by irradiation have recovered.

While our investigations were being pursued, it seemed pertinent to review the literature in an effort to find out what is known and what is surmised regarding the mechanisms involved in the irradiation of inflammatory conditions. We were particularly interested in obtaining information in regard to the effects of irradiation on bacteria, on blood supply to the involved area, on the leukocytes, and on antibody production and the establishment of immunity.

Mechanisms Involved in Irradiation of Inflammations. *Effects of Irradiation Upon Bacteria.* Korb,⁵ working with high voltage Roentgen rays, reported that doses as high as 22,000 r had no effect upon cultures of tubercle and colon bacilli. When rays generated at 50 K.V. were employed, however, these same bacteria were killed with much smaller doses. Korb also found that bacterial radio-sensitivity increased markedly with increases in the temperature at which bacteria were exposed to radiation.

This work summarizes well the comprehensive literature concerning the effects of irradiation upon bacteria that has accumulated since the pioneer work of Wolfenden and Ross¹⁰ in 1898. Unfortunately, most of these early experiments were inadequately controlled. Accurate calibration and the r unit were yet to be developed. In spite of these deficiencies, the bactericidal effects of huge doses of irradiation, the greater lethal effects of long wave length rays and the increased radio-sensitivity of bacteria with rises in temperature were adequately demonstrated before Korb's report appeared in 1933.

Effect of Irradiation Upon the Host. Possibly the main action of irradiation on infections is upon the blood supply. An increased circulation to the treated area is achieved which allows an influx of a greater amount of antibodies and neutrophils, and at the same time carries away more of the cellular débris and toxins which

accumulate locally as the result of bacterial growth. Some bacteria may be directly influenced by irradiation but it is probable that such an effect is not enough to be significant. It is also stated that irradiation increases the alkalinity of the tissues irradiated. Apparently an alkaline medium may be ideal for neutrophils, whereas the lymphocytes are more readily attracted toward an acid medium, such as occurs in certain chronic infections.

Irradiation is believed to affect complex protein molecules and may, by changing the structure of the toxin molecules, produce detoxification of the poison. Such a premise is theoretical but because irradiation does change the molecular structure of proteins elsewhere it may also affect the toxins of bacterial origin. Irradiation also changes the albumin-globulin ratio in the tissues. Ordinarily, the albumin fraction is higher than the globulin but irradiation raises the globulin in this ratio. The latest concept is that antibodies are specific globulin fractions and therefore anything that raises the globulin might also raise the antibodies. It is fairly well established that irradiation raises the antibodies and increases the bactericidal power of the blood. This is only true, however, when small doses such as are given in infections are employed. Larger doses produce a reverse reaction.

The function of the neutrophil is to destroy bacteria and this it accomplishes by means of an enzyme. The bacteria frequently kill the neutrophils, but even in death, this cell gives off a proteolytic enzyme which does not affect the bacteria but does produce liquefaction necrosis. Desjardin¹ believes leukocytic degeneration is of paramount importance in local immunity because it increases local phagocytosis.

Increased local immunity is usually attended by increased general body immunity. Irradiation probably favors this response, as numerous investigators have demonstrated increased bactericidal responses which last 3 to 5 days following small doses of irradiation. Long exposures and high intensities are known to depress rather than augment these favorable responses. The reticulo-endothelial system and the albumin-globulin ratio apparently are also favorably influenced by small doses of low voltage rays.

Experimental Data. For the production of lobar pneumonia in dogs, we used the same technique as that which we previously employed when animals similarly infected were treated with artificial pneumothorax.⁷

Method of Production of Lobar Pneumonia in Dogs. The method employed by us differed in a few details from that used by Robertson and his coworkers. After anesthetization the dogs were bronchoscoped, a No. 8 F. soft rubber catheter was passed through the bronchoscope into the bronchus supplying the lower lobe of the lung desired, and 1 cc. of potato starch paste containing 0.06 cc. of sedimented, virulent pneumococci was injected through the catheter. Two syringe barrells of air were then injected into

the catheter to disperse the starch paste throughout the lobe of the lung supplied by that bronchus. The details of our technique were as follows:

1. *Dogs.* Healthy dogs, either male or female, of average weight of 10 kg. were used.

2. *Pneumococci.* Strains (Types I (37 animals) and III (8 animals)) virulent for mice were used. These organisms were subjected to repeated passage through mice during the course of the experiment. All cultures used for inoculation were in the phase of active growth.

3. *The starch-broth mixture* advocated by Robertson and his coworkers was used.

4. *Anesthetization.* In order to obtain anesthesia with just enough relaxation necessary to permit bronchoscopy as well as the requisite fall in temperature for the establishment of the pneumonia, a preliminary injection

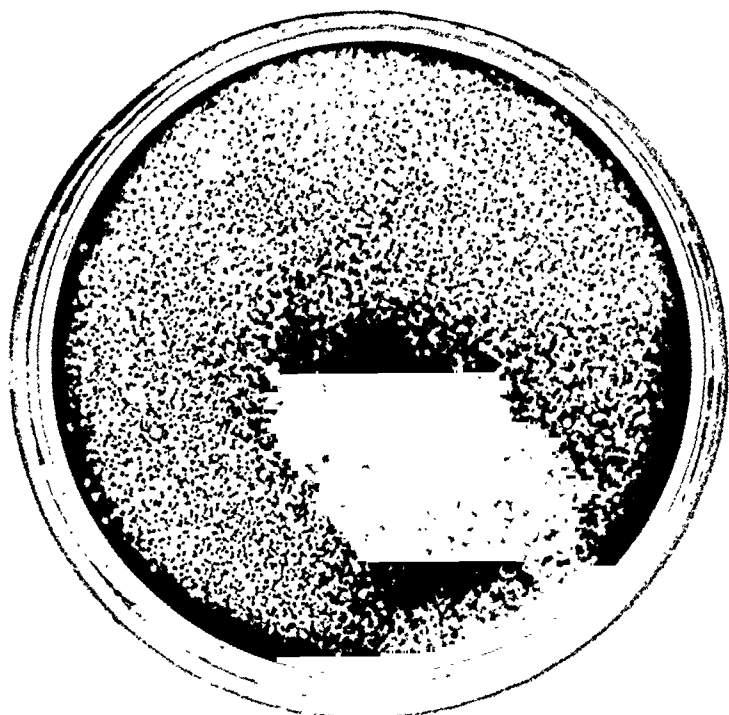


FIG. 1.—Dog 302 (control). Colonies from blood culture (2 cc.) on second day of disease. Died on fourth day.

of morphine sulphate (6 mg. per kg. B.W.) was given. This was followed in 30 minutes by the intraperitoneal injection of 15 mg. of sodium amytal per kg. body weight. About 15 minutes after the injection of the sodium amytal, bronchoscopic instillation of the culture was made.

5. *Postanesthetic Care.* As the dogs had a subnormal temperature for several hours because of the anesthesia, they were placed in a warm room, lying on the side where the starch paste culture was introduced.

6. *After Care.* The dogs were allowed the liberty of their cages and given daily one plentiful supply of cooked scraps and fresh water.

In this investigation we induced experimental pneumonia by the technique which we have described in 45 dogs, 26 of which were treated with Roentgen rays and 19 served as controls. Although

the technique was identical to that employed 6 years ago, at which time 5 of the 18 control animals recovered, none of the control animals in the present series survived.

TABLE 1.—RESULTS OF ROENTGEN TREATMENT OF ARTIFICIALLY INDUCED PNEUMONIA. GROUP I (80 K.V.).

Dog No.	Treated or control.	Pneumo. type.	Blood culture.	Amount of irradiation given and time given after pneumonia was induced.			Result.
				1st day.	2d day.	3d day.	
421 . . .	Treated	I	105*	Died 3d day
422 . . .	Treated	I	70	70	...	Died 3d day
420 . . .	Control	I	105	Died 2d day
417 . . .	Control	I	105	Died 2d day
260 . . .	Treated	I	105	105	Died 7th day
261 . . .	Treated	I	105	70	Died 8th day
262 . . .	Control	I	Died 2d day
263 . . .	Control	I	++++	Died 9th day
300 . . .	Treated	I	++++	105	105	...	Died 6th day
302 . . .	Treated	I	++++	105	105	...	Died 4th day
299 . . .	Control	I	++	Died 6th day
201 . . .	Control	I	++++	Died 6th day
381 . . .	Control	I	++	Died 2d day
382 . . .	Control	I	+	Died 2d day
383 . . .	Treated	I	0	105	105	...	Died 4th day
384 . . .	Treated	I	0	105	105	...	Died 6th day
421 . . .	Treated	I	++	120	120	...	Died 2d day
422 . . .	Treated	I	0	120	120	...	Died 2d day
424 . . .	Control	I	0	Died 1st day
425 . . .	Control	I	+	Died 2d day

* "r" measured in air.

TABLE 2.—GROUP 2 (135 K.V.).

Dog No.	Treated or control.	Pneumo. type.	Blood culture.	Amount of irradiation given and time given after pneumonia was induced.			Result.
				1st day.	2d day.	3d day.	
519 . . .	Treated	I	+	150	124	...	Recovered
520 . . .	Treated	I	0	150	124	...	Died 6th day
594 . . .	Treated	I	200	Died 6th day
595 . . .	Control	I	Died 1st day

The virulence of the infecting agent is shown in Figure 1, which illustrates the severity of the blood stream invasion which occurred in 5 of the 25 dogs on which blood cultures were taken.

The dogs were divided into 3 groups in accordance with the dosage of Roentgen rays which were used to treat them.

Group 1: These dogs were treated with rays generated at 80 K.V. and 5 ma., filtered through 5 mm. Al at a T.S.D. (target skin distance) of 30 cm.; portal, 20 by 20 cm., directed laterally into the affected lung.

This group included 10 irradiated animals and 10 controls. In the control series the average period of survival after induction of pneumonia was 3.4 days. The average period of survival in the

TABLE 3.—GROUP 3.

Dog No.	Treated or control.	Pneumo. type.	Blood culture.	Amount of irradiation given and time given after pneumonia was induced.			Result.
				1st day.	2d day.	3d day.	
614 . . .	Treated	I	200	Died 2d day
615 . . .	Control	I	Died 2d day
314 . . .	Treated	I	+	200	160	...	Died 28th day
315 . . .	Control	I	Died 1st day
316 . . .	Treated	I	+	160	120	...	Recovered
317 . . .	Treated	I	++++	160	120	...	Died 7th day
383 . . .	Treated	I	0	240	160	...	Recovered
384 . . .	Control	I	+	240	120	...	Died 3d day
385 . . .	Treated	I	+	240	160	...	Recovered*
387 . . .	Treated	I	200	160	...	Died 3d day
481 . . .	Treated	I	200	160	107	Recovered
482 . . .	Treated	I	200	160	107	Died 17th day
483 . . .	Control	I	Died 3d day
558 . . .	Control	III	Died 2d day
559 . . .	Treated	III	200	120	...	Died 3d day
560 . . .	Control	III	Died 2d day
561 . . .	Treated	III	200	Died 3d day
587 . . .	Control	III	+	Died 1st day
588 . . .	Treated	III	0	200	120	120	Recovered
589 . . .	Control	III	+	Died 4th day
590 . . .	Treated	III	+	200	120	...	Died 5th day

* Sacrificed 38th day.

animals treated with radiation was 4.5 days. There were 6 animals with positive blood cultures in the control group and 3 in the irradiated group. None of the dogs recovered.

Group 2: This group comprised only 4 animals because it was decided after this small group was treated to increase the dosage of irradiation without further delay. Three of these dogs were treated with rays generated at 135 K.V. and 8 ma. filtered through 25 cm. Cu + 1 mm. Al at a T.S.D. of 30 cm. One of the treated animals recovered.

Group 3: These dogs were treated with rays generated at 200 K.V. and 20 ma., filtered through 0.5 mm. Cu + 1 mm. Al at a T.S.D. of 50 cm.; portal, 20 by 20 cm., directed laterally into affected lung.

This group included 13 irradiated and 8 control animals. Three of the control and 5 of the treated dogs had positive blood cultures. The average survival period in the control series was 2.1 days. The average survival period in the irradiated animals which succumbed was 8.5 days. Five of the animals treated with Roentgen rays survived.

The results of the entire group are summarized in Table 4.

TABLE 4.—SUMMARY OF RESULT OF ROENTGEN TREATMENT OF ARTIFICIALLY INDUCED PNEUMONIA.

	Group 1 (80 K.V.).	Group 2 (120 K.V.).	Group 3. (200 K.V.).	Summary.
<i>Control Series:</i>				
Total number	10	1	8	19
Positive blood cultures	6	..	3	9
Average survival in days	3.4	1	2.1	2.9
Number recovered	0	0	0	0
<i>Irradiated Series:</i>				
Total number	10	3	13	26
Positive blood cultures	3	..	5	8
Average survival in days of those which				
died	4.5	6	8.5	6.2
Number recovered	0	1	5	6

Pathology.* The microscopic appearance of lung sections taken from the control animals dying within the first 4 days revealed cellular changes compatible with the acute phase of pneumonic infiltration, namely, congestion, edema, hemorrhage, and neutrophil infiltration. About one-half of the sections showed evidence of atelectasis. In 1 control animal that lived 9 days, the histologic appearance was that of a more chronic subsiding phase of pneumonia with marked round-cell infiltration.

In the irradiated animals the degree of congestion and hemorrhage was essentially comparable to that noted in the controls. Edema and atelectasis were less marked. Of interest in the treated group was a relative increase in round-cell infiltration associated with a decrease in the neutrophils. In general, the pneumonic process in the treated animals seemed to have progressed beyond the acute stage which characterized the control group.

Summary and Conclusions. Beneficial results based chiefly on clinical impressions and favorable case reports have been claimed for Roentgen therapy of lobar pneumonia. The lack of experimental evidence confirming or disproving these impressions impelled us to study the effects of Roentgen therapy in experimentally produced lobar pneumonia in dogs.

* We are indebted to Dr. George White and Dr. Dale R. Coman for the interpretation of the pathological sections.

Forty-five dogs were given lobar pneumonia, 26 of which were treated by irradiation and 19 served as controls. When the dosage of Roentgen rays was increased to that used in Group 3, 5 of the 13 treated animals survived.

Our results justify the conclusion that when sufficient dosage of irradiation is used in the treatment of experimental lobar pneumonia in dogs there is definite evidence of a trend toward survival.

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A FAMILY OUTBREAK OF PNEUMOCOCCUS TYPE I INFECTIONS.*

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It is well known that as many as 60% of healthy individuals may harbor pneumococci in the nasopharynx. Smillie's study^{20a} of the seasonal variation of the carrier state revealed that a marked change in the percentage of pneumococcus carriers occurs from month to month; only 17% of normal individuals in this study were carriers in July, whereas 66% were carriers in March. The most prevalent carried types are Types III, VI, VIII, XVIII and XIX. On the other hand, Types I, II, V, and to a lesser extent VII, are infrequently encountered except in patients with pneumonia and in their immediate family contacts. Smillie and Leeder²¹ have shown that about 20% of family contacts of Types I and II pneumonia have the homologous strain in the nasopharynx, whereas only 2% of hospital contacts are so infected. When there is an epidemic of colds in the family, the incidence of homologous Type I or II carriers may be very much higher. Bunim and Trask⁶ have

* This investigation has been conducted under a grant of the Josiah Macy, Jr., Foundation.

observed that the increase in the incidence of carriers of pneumococci was related to heterologous as well as to homologous types, and was also related to the youth of the subject and to the presence of symptoms of infection of the upper respiratory tract in the younger subjects.

Pneumonia may be caused by pneumococci which have been carried by the individual or by pneumococci newly acquired from a case of pneumonia or from a healthy carrier. Before the subdivision of pneumococci into types, it was supposed that most pneumonias were of autogenous origin, but with the additional evidence made possible by extension of knowledge regarding the different types,⁷ it has become apparent that a good majority of the cases of pneumonia result from direct or indirect contact with a previous case.

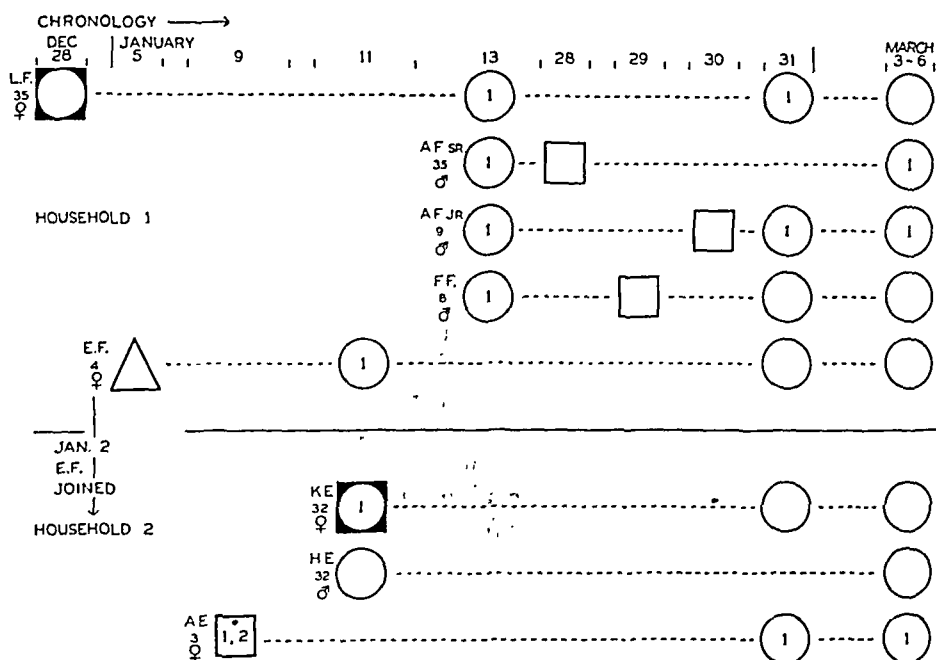
In 1928, however, Griffith¹² demonstrated that S forms of pneumococci could be transformed from one specific S type into other specific S types through the intermediate stage of the R form. He suggested that from the Group IV pneumococci in the nasopharynx are derived Types I and II during the development of pneumonia in the individual, and that during convalescence these types revert to the Group IV varieties from which they came. "The first essential is a situation in which it (the pneumococcus) can multiply, unchecked by the inhibitory action of a healthy mucous membrane. In the nidus thus formed the pneumococcus gradually builds up from material furnished by its disintegrating companions an antigenic structure with invasive properties sufficient to cope with the resistance of its host."

Griffith's observations concerning the transformation of types were confirmed *in vivo* by Neufeld and Levinthal¹⁵ and by Dawson,^{8a,b} and *in vitro* by Dawson and Sia⁹ and by Alloway.¹ Barnes and Wight² have reported the spontaneous transformation of pneumococcus Type V cultures into Type II. It seems certain that transformation of types can occur, but its relative importance in the spread of pneumonia is difficult to assess.

Various epidemics of specific types of pneumococcus pneumonia have occurred. Type I epidemics have been reported in a State Hospital,²² and in municipal lodging houses,³ and in a small village.¹⁴ Outbreaks of Type II pneumonia have been seen in a Veteran's Hospital,^{20b} and in a camp of the Civilian Conservation Corps.¹³ An epidemic of colds, bronchitis, and pneumonia due to Type V pneumococci has been described in a children's home.¹⁸

The intimate contact within family groups is particularly conducive to the spread of pneumococci, but the development of multiple cases of pneumococcic pneumonia within a short period of time in a family is infrequent. Nevertheless Tilghman and Finland²³ were able to collect a series of 33 families in which 2 or more members, ill of pneumococcic infections, were admitted to the Boston City Hospital during a 15-year period. Brown and Finland⁴ have

recently described a family in which 9 of 11 members had infections with Type V pneumococci and a tenth member carried the same organism while apparently remaining free of symptoms. Benjamin, Ruegsegger and Senior³ record 3 instances of simultaneous infections within families, and 3 instances of delayed homologous infection apparently arising from a family carrier who had recovered from pneumonia and returned home. They suggest the advisability of taking material for culture from the nose and throat of each patient convalescing from pneumonia before discharge from the hospital. We have observed several instances in which 2 members of the same family were admitted to Bellevue with pneumonias



♦ NUMBERS REPRESENT PNEUMOCOCCUS TYPES

◼ = PNEUMONIA

◻ = UPPER RESPIRATORY INFECTION

△ = INTESTINAL GRIPPE

○ = THROAT CULTURE

CHART 1.—Type I pneumococcus epidemic in a family.

of the same type. Recently a male attendant on a medical ward was taken ill at home with Type V pneumonia. He was cared for during the 2 days which elapsed before his admission to the hospital by his wife, also an attendant. Two days after his admission his wife was also admitted with Type V pneumonia. Both recovered. In furthering knowledge concerning the epidemiology of pneumococcic infections, information derived by studying family outbreaks is of value. For this reason we are here reporting an instance of pneumonia and a series of respiratory infection in a family of 5 members, all of whom were found to be carriers of Type I pneumococci, and the subsequent spread of this pneumococcus to

a sister's family, resulting in another case of Type I pneumonia (in the sister) and a respiratory infection associated with the finding of the organism in the throat (in a daughter). Certain immunologic observations were made, and the carrier state of members of both families was followed over a period of time (Table 1).

Case Report. L. F., a housewife, aged 35, suffered from general malaise and nasal stuffiness about Christmas time, 1939. On December 28 she experienced a shaking chill, which was followed by pain in the right side of the chest, cough with expectoration of rusty sputum, and fever. She was treated at home by her family physician as a case of lobar pneumonia. No typing was done. With sulfapyridine therapy, her temperature fell promptly and she made an uneventful recovery.

On the fourth, sixth, and eleventh days of her illness, the patient was visited by her sister, K. E., also a housewife, aged 32, who lives some 20 miles distant in another section of New York City. On the second visit, the 4-year-old daughter, E. F., in the household was taken to K. E.'s home, in order to relieve the family congestion. Here the child played and lived with A. E., the 3-year-old daughter of the second family.

On January 5, E. F. suffered a gastro-intestinal upset characterized by malaise and continued vomiting but no fever. She was considered to have a mild "intestinal influenza" which was prevalent in the vicinity at the time. Physical examination was negative. This illness lasted 5 days. On January 9, her cousin, A. E., became ill with a fever of 103.4° , vomiting and malaise. Physical examination was unrevealing except for a mildly inflamed pharynx. A throat culture was taken, and revealed Type I and Type II pneumococci. No further signs developed and her temperature was normal within 48 hours on symptomatic treatment. Because her father is a physician in contact with pneumonia patients, it was at first considered that he was probably a carrier of these organisms, but his throat culture failed to reveal pneumococci of any type.

On January 11, K. E. suddenly became ill with a temperature of 103° and vomiting, followed by cough, expectoration of rusty sputum, and pain in the right side of the chest. Type I pneumococci were directly isolated from the sputum, and from the combination of a typical history (lacking only a chill) and the isolation of a Type I pneumococcus from the sputum, a diagnosis of pneumonia was made. A blood culture was obtained and sulfapyridine therapy begun. A leukocyte count revealed 29,000 cells per c.mm. She was promptly taken to the New York Hospital, on the service of one of us (N. P.). On the same day, before sending the child home, a throat culture was taken on E. F.; it was positive for Type I pneumococci. The patient (K. E.) failed to respond to sulfapyridine therapy, however, and after 24 hours was given 100,000 units of concentrated Type I rabbit serum, with immediate defervescence. Because of inability to retain sulfapyridine and failure to respond to the drug, another 100,000-unit dose of serum was given as a precaution on the following day, at which time physical signs suggesting consolidation were present over the right lower lobe.

On January 13, throat cultures were obtained from the first patient, L. F., and the remaining members of her family. Cultures positive for Type I were obtained from her, from her husband, and from 2 small sons. The patient herself, now convalescent, was found to have a positive Francis test for Type I.

Because of the possibility that the failure of K. E. to respond to sulfapyridine could have been due to picking up the organism directly or indirectly from her sister at a time when it had become

sulfapyridine-fast, a culture of the organism isolated from the sputum on January 11 was sent to Dr. Whelan D. Sutliff, Director of the Pneumonia Control Division of the New York City Department of Health, along with the cultures of all of the other members of both branches of the family, for tests for sulfapyridine fastness. These tests failed to reveal abnormal resistance to sulfapyridine, and this was confirmed subsequently by Dr. Colin McLeod of the Rockefeller Institute for Medical Research.

On January 31, a second set of throat cultures was obtained from all of the individuals who had shown pneumococci, except A. F., Sr., the husband of the first pneumonia patient. Three of these 6 cultures were still positive for Type I (L. F., A. F., Jr., and A. E.). The latter had by this time lost her Type II organisms. The 3 individuals not previously ill (A. F., Sr., in Pittsburgh; A. F., Jr., aged 9 and F. F., aged 8) now had upper respiratory infections with fever. On March 3, a complete set of throat cultures was taken from the 8 members of the two families. Three were still positive for Type I (A. F., Sr., A. F., Jr., and A. E.). On April 11, a throat culture on A. E. showed no pneumococci.

Comment. As the events as outlined above proceeded, the nature of the epidemiology involved became clear. It is apparent, in spite of the fact that no pneumococcus typing was undertaken on L. F. or her family when she first became ill, that all of the members of her family were invaded by the Type I pneumococcus and that only 1 member contracted pneumonia. Just which member introduced the organism cannot be stated with certainty. It is possible that the husband (A. F., Sr.) was responsible; he had recently (December 23) returned from Pittsburgh, where pneumonia is prevalent, but had not been in contact with an actual case of pneumonia as far as he knew. Any of the family, however, could have been the first to harbor the organism.

The transference of the Type I pneumococcus to the other branch of the family was probably mediated through the boarding out of the child, E. F., in the second household. It is possible that the infection was transmitted directly by the first pneumonia patient to her sister, who subsequently became the second case of pneumonia, but (1) transmission of the disease by this means is not usual; (2) the daughter, A. E., in the second household, who was in intimate contact with E. F., was found to harbor a Type I pneumococcus 2 days before pneumonia developed in her mother; and (3) during the visits of the sisters care was taken by K. E. to remain away from the bed, and by L. F. to cover her mouth when coughing.

The relationship of the carrier state to the gastro-intestinal upset of the daughter, E. F., and of the upper respiratory infections of her brothers, her father, and her cousin, is not entirely clear. Smillie^{20a} believes that there is some relationship of epidemics of family colds to the presence of homologous types of pneumococci in contacts of

lobar pneumonia due to Types I and II. One of the boys, however, did not show the organism in his throat culture at the time he developed the respiratory infection.

Where A. E. acquired the Type II as well as Type I organisms is also not clear. Her father, who had been in contact with several Type II pneumonias, was a possible source, though his throat cultures showed no pneumococci.

Pneumococci of the rarely-carried types usually disappear from the throats of convalescent pneumonia patients or their family contacts within 30 days.^{14,15} Our first pneumonia patient carried Type I pneumococci for at least a month after the onset of her illness, in spite of sulfapyridine therapy, and lost them sometime during the next month. The second pneumonia patient had no pneumococci in her throat 3 weeks after the onset of her illness. Three of the carriers (Table 1) harbored the organism for at least 8 weeks, 1 of them (A. E.) in spite of a 3-week stay in Florida where, it was hoped, the greater opportunity to be outdoors and in the sunshine would help her to discard the organism.

Immunologic Observations. Studies of carriers and non-carriers have shown that homologous type-specific antibodies may develop in a large percentage of healthy contact carriers of disease-producing pneumococci.¹¹ We have carried out agglutination tests by the microscopic method⁶ on most of the members of the families described. The pneumonia patients developed antibodies, as might be expected from the fact that they recovered. The two most persistent carriers in the first family developed demonstrable increases in their antibodies over the course of the 2 months during which they were known to be carriers. Data on other members of the families are incomplete.

Summary and Conclusions. 1. A family outbreak of infections which included 3 cases of upper respiratory disease, a case of pneumonia and a gastro-intestinal upset, in a family of 5 individuals, all of whom were shown to harbor Type I pneumococci in the nasopharynx, is reported.

2. The apparent transfer of the organism to a sister's family with subsequent outbreak of an upper respiratory infection in 1 individual and a Type I pneumonia in another is described.

3. Before boarding out a child from a home where there is a case of pneumonia, a throat culture which is negative for the type of pneumococcus causing the patient's illness is recommended.

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THE ABSORPTION, DISTRIBUTION, AND EXCRETION OF 2-SULFANILAMIDO PYRIMIDINE (SULFAPYRIMIDINE, SULFADIAZINE) IN MAN.*

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SEVERAL new sulfonamide compounds described within the past year have warranted clinical trial because of their therapeutic effectiveness against experimental pneumococcal infections and relatively low degree of toxicity in animals. 2-sulfanilamido pyrimidine (sulfapyrimidine, sulfadiazine) described by Roblin, Williams, Winnek, and English⁷ is among the more promising of the new compounds. Bacteriologic and pharmacologic studies reported by these authors and by Feinstone, *et al.*² indicate that sulfapyrimidine is effective against experimental streptococcal or pneumococcal infections in mice, and also that it is readily absorbed from the gastrointestinal tract in this species. The therapeutic activity of the compound in preliminary mouse tests was greater than that of sulfanilamide, sulfapyridine, or sulfathiazole.

Since the intelligent use of these drugs requires an understanding of their behavior when administered to man, we have investigated the fate of sulfapyrimidine‡ in a group of patients. Two series of experiments, one dealing with the fate of a single dose and the other with the response to multiple doses are reported in the present paper.

* Aided by a grant from the American Philosophical Society.

† Detailed for this and related studies on pneumonia by the Pennsylvania Department of Health, Pneumonia Control.

‡ We are indebted to Dr. Howard Hogan, Nepera Chemical Company, Yonkers, N. Y., for the sulfapyrimidine used in this study.

Methods and Materials. Sulfapyrimidine was determined by the method of Bratton and Marshall.¹ Because of the low solubility of the drug in water, about 10 mg. per 100 cc. solutions for standards were prepared by addition of approximately 4 cc. of normal sodium hydroxide solution to 100 mg. of sulfapyrimidine crystals. Water was then added to bring the volume to 500 cc. Solutions so prepared were stable for at least a month in the refrigerator. Recovery of drug added to blood deviated from the theoretical only to a negligible extent. Other methods employed in this study were the same as those used previously.⁵

The effects of the administration of single doses of sulfapyrimidine were studied in a group of 12 adult patients convalescing from various medical conditions and showing no evidence of gastro-intestinal, hepatic, or renal disease. The effects of continued administration of the drug were studied in 20 patients suffering from pneumonia and in 4 with other disorders.

Results. ABSORPTION AND DISTRIBUTION. 1. *Fate of a Single Dose.* Each of 12 patients was given 3 gm. of sulfapyrimidine as a single dose by mouth shortly after a breakfast consisting of cereal, bread, milk, and canned fruit. Within 2 hours, the average concentration of free drug in the blood was 2.3 mg. per 100 cc., while the highest level reached at this time was 4.6 mg. per 100 cc. (Table 1). The concentration of free drug continued to rise in all patients, reaching an average concentration of 4 mg. per 100 cc. between 4 and 8 hours (Table 2). During this period the concentration showed little change, and, presumably, remained near this level for some additional hours, since after 24 hours an average concentration of 2.2 mg. per 100 cc. was present. Only 2 patients showed less than 2 mg. per 100 cc. in blood in the 24-hour sample, and after 48 hours concentrations near 1 mg. per 100 cc. were found in all except 3 patients.

An average of 0.5 mg. per 100 cc. of the drug was present in acetylated form in this group of patients throughout the 48-hour period, and indeed the concentration of acetylated drug remained remarkably uniform. The highest concentration of acetylated sulfapyrimidine was 1 mg. per 100 cc. An increase in percentage of acetylation during the later periods was due to a decrease in the concentration of free drug while the acetylated form remained practically constant.

Excretion of sulfapyrimidine in the urine was comparatively slow, the average excretion being less than half of the administered drug within 24 hours, as compared with 60% to 90% excretion following ingestion of an equivalent amount of sulfathiazole.⁵ Individual figures for sulfapyrimidine excretion varied between 10% and 60% in 24 hours. In 48 hours, 47% to 85% of the drug was excreted. The patient excreting only 10% in 24 hours (Case 5) apparently absorbed much less drug than the others and also showed low concentration in the blood. Relatively low concentrations of acetylated sulfapyrimidine were present in the urine of these patients. The highest concentration was 40 mg. per 100 cc., the average 22 mg. per 100 cc. During the first 24 hours an average of 23% of the drug was excreted as the acetyl derivative. Crystals closely resem-

6	H.A.	2	2.6	3.1	16.0	3.4	4.0	50.0	62.5	20.0	5.0	15.6	68.0	98	1.00
7	W.T.	2 4 6 8 24 48	4.6 5.1 5.2 4.5 2.8 0.8	5.2 5.5 6.0 2.8 1.2	11.5 9.0 13.4 33.3	5.7	6.4	100.0 125.0 60.0 40.0	127.5 155.0 100.0 67.5	22.2 20.0 40.0 40.0	5.7 20.8 50.6 72.3		59.0	95 135 88 115	0.56 1.24 0.92 0.67
8	J.F.	2 4 6 8 24 48	3.0 5.0 4.5 2.5 1.0	3.3 5.3 4.7 2.7 1.0	9.0 6.0 4.5 7.5 0.0			35.0 75.0 60.0 35.0	42.5 92.5 80.0 50.0	17.6 22.3 25.0 30.0	3.1 12.2 28.7 47.0		 67 105	0.92 1.17 0.65 0.76
9	F.G.	2 4 6 8 24 48	2.5 4.7 4.6 4.5 2.0 1.0	2.8 5.0 4.8 2.4 1.3	11.0 6.0 4.2 16.6 23.0			25.0 40.0 45.0 25.0	25.0 47.5 57.5 35.0	0.0 15.8 21.7 28.6	5.2 22.7 51.1 74.1		 70 60	2.58 3.75 1.76 1.33
10	C.S.	2 4 6 8 24 48	2.0 5.4 5.5 4.0 2.3 0.9	2.0 5.6 5.8 5.3 2.5 1.1	0.0 3.6 5.2 7.5 8.0 18.0			20.0 137.5 75.0 30.0	25.0 150.0 95.0 35.0	20.0 8.6 21.0 12.4	2.2 19.7 45.6 65.7		 133 130	1.08 1.46 0.85 1.20
11	R.D.	2 4 6 8 24 48	2.5 4.4 5.5 5.3 2.6 1.2	2.7 4.7 6.0 5.7 3.0 1.6	7.4 6.4 6.6 7.0 13.3 25.0										
12	J.L.	2 4 6 8 24 48	1.6 3.0 3.5 3.5 3.4 1.6	2.4 3.5 4.0 4.0 4.0 2.3	33.3 14.3 12.5 14.4 30.0	4.4	4.7								

* Cerebrospinal fluid at 6 hours was 1 mg. per 100 cc. of free drug.

bling those of sulfapyrimidine were detected in the urinary sediment of one patient. The washed sediment contained both free and acetylated drug.

Renal clearance of free sulfapyrimidine of 6 patients averaged 31 cc. of serum per minute* based on the period between 4 and 8 hours. Patient C. J. was omitted from calculation of averages because of a subnormal urea clearance. The clearance of acetyl-sulfapyrimidine was much higher than that of the free drug and averaged 59 cc. per minute between 4 and 8 hours. Under somewhat different conditions⁹ the renal clearance of sulfathiazole has been found to be 43 cc. of serum per minute for free and 55 cc. per minute for acetylated, while for sulfapyridine the corresponding figures were 23 and 58 cc. of serum per minute.

TABLE 2.—FATE OF SINGLE DOSE (3 Gm.) OF SULFAPYRIMIDINE.
(Averages of 12 Patients.)

Time, hours.	Blood.			Urine.			
	Free (mg. per 100 cc.)	Total	Acetylated, %.	Free (mg. per 100 cc.)	Total	Acetyl- ated, %.	% of dose excreted (cumu- lative).
2	2.3	2.7	15.0				
4	3.9	4.4	11.3	33.7	43.5	23	4
6	4.1	4.6	10.9				
8	4.0	4.5	11.1	78.5	98.5	20	18
24	2.2	2.7	18.5	56.0	76.5	26	44
48	1.0	1.4	28.0	32.4	47.0	31	68

In 10 specimens analyses were made of both whole blood and serum. Table 1 shows sulfapyrimidine to be distributed almost equally between cells and serum when allowance is made for difference in water content. In this it resembles sulfanilamide and sulfapyridine but differs from sulfathiazole which penetrates red blood cells to a lesser extent.⁶ Identical values were found in serum and plasma.

2. *Multiple Dosage.* In Table 3 are shown representative blood studies of 20 patients suffering from pneumonia who received sulfapyrimidine. Most patients were given an initial dose by mouth of 3 gm. which was then followed by 1 gm. at 4-hour intervals. Blood was collected approximately 2 hours after the last previous dose. In 2 patients (Cases 13 and 19) because of vomiting in association with high levels of the drug in the blood, the dose was reduced by half. Patients 16, 18, 22, and 31 likewise received 3 gm. daily during all or part of the treatment period. The average concentration of free sulfapyrimidine was 9.5 mg. per 100 cc. when 6 gm. were given daily. Concentrations ranging from 4.4 to 19 mg. per 100 cc. were encountered. Six patients receiving 3 gm. daily showed lower

* No adjustment has been made for small urine volumes in calculating drug clearance. By clearance is meant the concentration of drug in urine divided by that in serum and multiplied by the urine volume in cc. per minute.

concentrations, averaging 5.7 mg. per 100 cc. and ranging from 2 to 11 mg. per 100 cc. The concentration of acetylsulfapyrimidine averaged 1.8 mg. per 100 cc. or 16% of the total when 6 gm. daily was given, compared with an average of 1.5 mg. per 100 cc. or 21% of the total when 3 gm. daily was given.

Analysis of urine collected while 5 patients were receiving sulfapyrimidine showed concentrations varying between 40 and 350 mg. per 100 cc. of free drug with an average of 136 mg. per 100 cc., while acetylsulfapyrimidine varied between 20 and 225 mg. per 100 cc. with an average of 62 mg. per 100 cc. An average of 32% of the drug was excreted in acetylated form. Between 18% and 200% of the total amount ingested during a day reappeared in the urine the same day, excretion exceeding the daily intake representing a carry over from preceding days. Excretion continued at a high rate for more than a day after the drug was discontinued.

3. *Sulfapyrimidine Concentrations in Various Body Fluids.* Table 4 shows the distribution of sulfapyrimidine in several body fluids other than blood, and, for comparison, the concentration in blood at the time the specimens were collected. It is evident that the pleural and peritoneal cavities are readily penetrated by sulfapyrimidine, concentrations of drug in fluids from these sources being only slightly less than in blood.

Cerebrospinal fluid likewise contained appreciable concentrations of sulfapyrimidine after 24 hours, during which repeated doses of the drug were administered. An average of 54% of the concentration of free drug in blood was present in the cerebrospinal fluid of 4 patients (Case 18, Table 3, included). Cerebrospinal fluid of Patient 1 (Table 1) contained 1 mg. per 100 cc. of free sulfapyrimidine 6 hours after ingestion of 3 gm.

Toxic Effects.—Table 3 depicts toxic effects noted in patients receiving multiple doses. Vomiting occurred in 3 patients. In 2, vomiting was controlled by decreasing the dosage from 6 to 3 gm. daily. One patient who vomited also showed dermatitis which necessitated stopping the drug. Both toxic manifestations disappeared within 24 hours after the drug was discontinued. No toxic effects were noted in the patients receiving single 3-gm. doses.

Comment. The behavior of sulfapyrimidine, in general, is quite similar to that of sulfapyridine, as may be expected from the similarity in structure of the two compounds. Sulfapyrimidine is absorbed readily from the gastro-intestinal tract and concentrations in blood considered to be effective are reached in 2 to 4 hours. The drug disappears from blood slowly and appreciable quantities remain in blood 48 hours after administration of a 3-gm. dose. Our observations in this respect agree with those of Plummer and Ensworth.*

* We are indebted to Drs. Plummer and Ensworth for the opportunity to consult their paper before publication.

TABLE 3.—EFFECT OF CONTINUED ORAL ADMINISTRATION OF SULFAPYRIMIDINE.

No.	Patient.	Day.	Sulfapyrimidine.								Remarks.
			Dose, gm.	Blood.			Urine.				
				Free, mg. per 100 cc.	Total, mg. per 100 cc.	Acetyl- ated, %.	Free mg. per 100 cc.	Total, mg. per 100 cc.	Acetyl- ated, %.	Daily excre- tion, gm.	
13	F.L.	1	4								Vomiting Vomiting
		2	6	9.0	11.0	18.2					
		3	5	9.2	11.2	17.8	40.0	100.0	60.0	0.8	
		4	3	6.4	8.3	23.0					
		5	3	6.6	8.8	25.0					
		6	3	11.0	12.0	8.2	75.0	135.0	48.0	1.9	
		7	1	50.0	87.5	43.0	1.3	
14	E.W.	1	4								
		2	6	8.4	9.0	6.6					
		3	6	13.0	16.0	18.7	150.0	200.0	25.0	1.1	
		4	6	7.6	9.0	15.5	350.0	575.0	41.0	4.5	
		5	6	7.0	8.0	12.3	275.0	350.0	21.0	2.3	
		6	2	175.0	250.0	30.0	2.2	
15	E.C.	1	4								
		2	6	7.0	7.6	8.0					
		3	6	8.4	9.2	8.7	60.0	80.0	25.0	1.9	
		4	6	9.4	11.0	14.5	175.0	215.0	19.0	2.5	
		5	6	9.0	10.0	10.0	150.0	180.0	16.0	1.7	
		6	2	7.4	8.4	12.0	225.0	275.0	18.0	4.1	
		7	85.0	100.0	15.0	1.5	
16	M.G.	1	3								Severe vomiting; dermatitis
		2	3	4.0	5.0	20.0	
17	B.E.	1	3								
		2	6	8.0	9.0	11.0					
		3	6	8.0	9.0	11.0					
		4	6								
		5	6	7.0	8.0	12.5					
		6	3	7.4	9.5	11.6					
18	G.C.	1	4.5								Sp. fl. free = 2.6; total = 2.8
		2	3	4.4	5.3	16.4					
		3	3	4.0	4.7	15.0	150.0	200.0	25.0	1.6	
		4	3	4.0	4.8	16.3	100.0	125.0	20.0	1.3	
		5	3	2.0	115.0				
19	M.J.	1	4								Vomiting
		2	6	11.7	13.0	10.0					
		3	6	15.0	16.5	9.1					
		4	4	12.0	13.2	9.6	
		5	3	6.4	7.0	8.6					
		6	3	6.0	7.0	14.3					
		7	3	7.0	8.0	12.2					
		8	3	6.7	7.4	9.4					
		9	3	9.6	10.3	6.8					
		10	3	7.5	8.4	17.1					
		11	3	7.0	8.0	12.3					
		12	1.5	9.0	10.5	9.9					
20	J.W.	1	5								
		2	6	8.7	9.5	18.2					
		3	5	7.5	9.0	16.6					
21	M.J.	1	3								
		2	6	6.7	9.5	30.0					
		3	6	14.0	15.0	7.0					
		4	6	8.0	10.0	20.0					
		5	4	5.5	7.3	40.0					

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TABLE 3.—EFFECT OF CONTINUED ORAL ADMINISTRATION OF SULFAPYRIMIDINE—Continued.

EFFECT OF CONTINUED ORAL ADMINISTRATION OF SULFAPYRIMIDINE IN MAN											
Sulfapyrimidine—Continued.											
No.	Patient.	Day.	Dose, gm.	Blood.			Urine.				Remarks.
				Free, mg. per 100 cc.	Total, mg. per 100 cc.	Acetyl- ated, %.	Free mg. per 100 cc.	Total, mg. per 100 cc.	Acetyl- ated, %.	Daily excre- tion gm.	
22	W.J.	1	3								
		2	4								
23	W.H.	1	5	3.0	4.0	25.0					
		2	6								
		3	1	13.4	19.0	29.0					
				15.6	22.0	29.0					
24	S.S.	1	5								
		2	6	6.0	7.0	14.3					
		3	6								
		4	5	9.0	10.0	10.0					
		5	..	2.3	3.0	23.3					
25	F.P.	1	4								
		2	6	6.0	7.0	14.3					
		3	6	7.0	7.7	9.1					
		4	5	6.8	7.3	6.9					
		5	..	2.0	2.8	29.0					
26	S.R.	1	4								
		2	6	14.5	16.7	13.2					
		3	6	16.6	18.0	7.7					
		4	2								
27	E.P.	1	4								
		2	7	7.4	8.3	7.7					
		3	6	10.0	12.0	17.0					
		4	6	13.0	14.0	7.1					
		5	3								
28	L.M.	1	6								
		2	6	4.4	5.0	12.0					
		3	6	7.0	8.0	12.5					
		4	6	6.0	7.0	14.3					
29	B.B.	1	4								
		2	6	7.0	7.8	9.8					
		3	6	12.0	13.3	9.9					
		4	6	13.3	14.3	7.0					
		5	4	10.0	11.0	9.0					
30	M.B.	1	4								
		2	6	5.6	6.4	12.5					
		3	6	8.0	9.0	11.0					
		4	6	5.0	6.0	16.3					
		5	3	4.0	5.0	20.0					
31	J.P.	1	4								
		2	6	5.0	6.0	16.3					
		3	4	9.0	10.0	10.0					
		4	7	12.0	14.3	14.3					
		5	6	15.0	18.0	16.3					
32	W.O.	1	3								
		2	6	8.0	9.5	15.8					
		3	6	15.0	18.0	16.7					
		4	4	19.0	22.0	13.6					
		5	4	12.0	13.0	7.7					
		6	3	8.0	9.3	14.0					
							85.0	175.0	51.4	1.6	
							125.0	225.0	40.0	2.1	
							125.0	175.0	28.6	2.0	

The concentration of acetylsulfapyrimidine in blood has been found to occur within the range of concentrations observed in studies of acetylsulfathiazole.^{3,5} In urine, statistical comparison indicates that the concentration of acetylated sulfapyrimidine is significantly lower than that of acetylated sulfathiazole. However, the number of patients studied is so small that considerable uncertainty remains in regard to the validity of this evidence.

Sulfapyrimidine readily enters the peritoneal and pleural cavities, and concentrations in ascitic fluid and pleural effusion were only slightly less than in blood. Concentrations of drug in spinal fluid were about 50% of the level in blood collected at the same time. In this respect the new drug is superior to sulfathiazole which penetrates into the cerebrospinal fluid to a much more limited extent.⁸ Sulfapyrimidine also penetrates into red blood cells far more readily than does sulfathiazole.⁶

TABLE 4.—SULFAPYRIMIDINE CONCENTRATION IN VARIOUS BODY FLUIDS.

No.	Patient.	Hours after initial dose.	Total dose, gm.	Blood (mg. per 100 cc.).		Body fluid (mg. per 100 cc.).	
				Free.	Total.	Free.	Total.
31	J.P.	72	14	9.0	10.0	<i>Pleural Effusion</i>	
		96	20	12.0	14.3	7.4	9.0
		120	26	15.0	18.0	10.0	14.0
						14.6	15.0
33	S.J.	18	8	10.0	10.8	<i>Ascitic Fluid</i>	
						9.6	10.0
						<i>Cerebrospinal Fluid</i>	
34	M.M.	24	9	9.3	10.4	4.4	5.0
35	C.J.	24	9	12.0	14.0	5.0	5.4
36	E.N.	24	9	4.6	5.0	3.0	3.5

Excretion of sulfapyrimidine in 24 hours following a single dose was about two-thirds that of sulfathiazole. The renal clearance of sulfapyrimidine was found to be less than that of sulfathiazole, but greater, apparently, than that of sulfapyridine. Clearance of the acetyl compounds was approximately the same for each of the three drugs. A tendency toward rapid accumulation of free drug in blood in the presence of even moderate impairment of renal function has been noted. It is our impression that this tendency is even more pronounced with the new drug than it is with sulfapyridine, and far more so than for sulfathiazole. Because of efficient absorption and relatively low rate of excretion, smaller dosage of sulfapyrimidine as compared with sulfathiazole is required to maintain a given concentration in blood.

Observation of 24 sulfapyrimidine-treated patients has revealed no evidence of severe toxicity. Vomiting occurred in 3, but was controlled in 2 when the drug dosage was halved. In the third, the vomiting was associated with dermatitis, both of which disappeared within 24 hours after the drug was discontinued. Plummer and Ensworth⁴ have reported the occurrence of a morbilliform rash in 1 patient receiving sulfapyrimidine.

Evaluation of the therapeutic effectiveness of sulfapyrimidine requires further clinical study, although experience with 30 patients suffering from pneumonia has indicated that the drug is active and that further trial is warranted.

Summary. 1. The behavior of 2-sulfonamido pyrimidine (sulfapyrimidine, sulfadiazine) when administered as a single dose or as multiple doses by mouth to humans resembles that of sulfapyridine more nearly than that of sulfathiazole.

2. Sulfapyrimidine is readily absorbed from the gastro-intestinal tract of most individuals.

3. Sulfapyrimidine is not excreted as readily as sulfathiazole and disappears from the blood slowly. Smaller quantities of the former are required to maintain a given level in blood.

4. Concentrations of acetylated drug found in blood did not differ from those previously observed in studies of sulfathiazole.

5. Sulfapyrimidine is present in peritoneal and pleural fluids in concentrations approximating those in blood. In cerebrospinal fluid, concentrations averaging 50% of the blood concentration have been found.

6. As regards toxicity, limited experience has revealed evidence that in man it is at least no greater than that of other drugs of this group now used in the treatment of pneumonia.

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THE BEHAVIOR OF THE BLOOD SEDIMENTATION RATE DURING AND AFTER FEVER THERAPY.

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The sedimentation rate of the red blood cells is one of the indications of the progress of two diseases that are being treated with artificial fever, rheumatoid arthritis and rheumatic fever. Further-

more, this test is at times of value in following the progress of Sydenham's chorea and gonococcal infections, two other diseases in which fever therapy is widely used. It is therefore important to know whether the fever itself changes the sedimentation rate, either during the period of elevated temperature or afterwards. If physically produced fever does alter the sedimentation rate, it would be necessary to wait for the effect of fever therapy to wear off before getting an accurate determination.

There is little in the literature as to the effect of fever used therapeutically on the blood sedimentation rate. Colinet¹ has reported, in some cases of rheumatism treated with short sessions of electropyrexia, a decrease in the sedimentation rate 24 hours after the fever. However, in many of his cases these values were about the same as before the fever session, so his results are not conclusive. Krusen,⁶ in a study of the effects of fever therapy on the blood, reported incidentally that sedimentation rates before and after fever therapy were approximately the same. In 100 cases the average sedimentation rate before fever therapy was 12.3 mm., and after fever 13 mm. The sedimentation times were also about the same before and after fever therapy—50.9 and 53.5 minutes, respectively.

We undertook this study to see if we could corroborate Krusen's work, and to amplify it.

Method. The 41 patients used in this study were given artificial fever in the hypertherms at the Philadelphia General Hospital for various diseases. Of the patients, 27 had general paresis, 4 rheumatoid arthritis, 3 gonococcal arthritis, 3 Sydenham's chorea, 2 ulcerative colitis, 1 rheumatic fever, and 1 multiple sclerosis. The temperatures used varied from 104° to 107° F. (rectal), depending on the disease for which they were being treated.

The sedimentation rate of the red blood cells was determined on specimens taken just before the patient was put into the cabinet. The temperature was normal at this time in practically all of the patients. The sedimentation rate was determined again 3 times: during the height of the fever, as soon after removal from the cabinet as the temperature had returned to normal, and the day after the fever treatment. The small Cutler tube (with 2.5% sodium citrate solution as the anticoagulant) was used in the determinations, chiefly because of its convenience. Readings were made every 5 minutes for 1 hour. What Cutler³ calls the sedimentation time as well as the sedimentation rate (or index) was determined when the rate was rapid enough so that this could be estimated. According to Cutler,³ the sedimentation time is the time in minutes at which the packing of the red blood cells has caused the sedimentation of the cells to slow to 1 mm. in 5 minutes. It is determined only if the rate is rapid, *i. e.*, in cases in which a diagonal or vertical curve is obtained if the 5-minute readings in millimeters are plotted against the time in minutes.

A great deal has been written on the various factors, aside from disease, that affect the sedimentation rate. However, the present tendency, as shown by the paper of Hambleton and Christianson,⁵

and by recent editorial comment,² is toward simplification of the test and disregard of the corrections that some workers have thought necessary for an accurate determination. Two of the variables that seem worth mentioning here are external temperature and cell volume. As to the first, it has been shown by various workers^{4,7} that the sedimentation rate increases with increase in the temperature of the surroundings at which the test is done, being appreciably higher at 37° C. (body temperature) than at room temperature and still slower at 10° C. In all of our tests the blood was allowed to assume room temperature before the determinations were made. Although the room temperature varied somewhat from week to week during the months that the tests were being done, the variations during any 24-hour period when the several determinations were done on any one patient were too small to cause an error greater than that of the method itself. Variations in room temperature were therefore disregarded. As to corrections for cell volume, we did not do hematocrit readings and make any corrections because any change in cell volume would be, for practical purposes, constant during the 24-hour period when the determinations were being done on any one patient. In any case, if failure to correct for cell volume introduced an error, this error was the same in all the determinations that were compared with each other.

Results. As was to be expected in a group of patients suffering from different diseases, the sedimentation rates differed considerably. The lowest rate was 3 mm. in 1 hour; the highest rate was 31 mm. But whether the initial reading was normal or increased, we found little variation in the sedimentation rates of any one patient's blood in the 4 determinations made. Often, the variation was only 1 mm. Usually, there was not more than 2 or 3 mm. variation, and the maximum variation was 6 mm. What slight variation there was, was not uniform, *i. e.*, in some patients the rate was 2 or 3 mm. faster during the fever, and in others it was slightly slower during the fever. This lack of a uniform trend in the variation shows, we believe, that whatever differences were obtained were not due to the fever, but were due to the errors inherent in the method itself.

The table summarizes the averages of the sedimentation rates of the 41 patients for each of the four determinations. In 24 cases the sedimentation rates were fast enough that the sedimentation times could be determined. The averages of these are given also.

TABLE 1.—AVERAGE OF BLOOD SEDIMENTATION RATES AND TIMES.

	Before fever therapy.	During fever therapy.	Immediately after fever therapy.	Day after fever therapy.
Average blood sedimentation rate: mm. per hour (41 cases)	17.8	18.9	17.4	19
Average blood sedimentation time in minutes (24 cases)	42	40	43	40

Summary and Conclusions. 1. Sedimentation rates were determined on 41 patients who were receiving physically induced fever in the hypertherm. Determinations were made before, during, immediately after, and the day after the fever treatment.

2. No significant variations in the sedimentation rates were found in these four determinations.

3. For practical purposes, physically induced fever used therapeutically does not affect the sedimentation rate.

4. An accurate determination of the sedimentation rate can therefore be made at any time during or after a fever session.

We wish to express our appreciation to the nurse-technicians, Miss Margaret Starr and Miss Pauline Baumgartner, who gave the fever treatments under our direction.

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BOOK REVIEWS AND NOTICES

SIMPLIFIED DIABETIC MANUAL with 163 International Recipes (American, Jewish, French, German, Italian, Armenian, etc.). By ABRAHAM RUDY, M.D., Associate Physician and Chief of the Diabetic Clinic, Beth Israel Hospital, Boston; Instructor in Medicine, Tufts College Medical School, etc. Introduction by DR. FREDERICK M. ALLEN. Pp. 216, 10 illustrations. Second Edition. New York: M. Barrows & Co., Inc., 1940. Price, \$2.00.

THIS book is, in the main, just another diabetic manual. Its language is simple and clear, perhaps a little more elementary than some of the other manuals, and thus perhaps more readily used by patients of limited education. Its discussions of the usual topics such as physiology, symptoms, diet and insulin, and the prevention and management of complications is quite adequate. A feature which distinguishes it from most of the other manuals is the especial consideration given to the religious and culinary customs of various nationalities in preparing diet lists and recipes. For instance, there are special regulations for the management of Jewish diabetics at the Passover and other holiday seasons. Recipes especially adapted to Armenian, Italian, Jewish, German, French, Swedish and Greek patients are given in detail. These recipes may sometimes be quite useful.

J. C.

HISTOPATHOLOGY OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEMS. By GEORGE B. HASSIN, M.D., Professor of Neurology, University of Illinois College of Medicine; Attending Neurologist, Cook County Hospital, Chicago. Pp. 554; 302 illustrations. Second Edition, revised and enlarged. New York: Paul B. Hoeber, Inc., 1940. Price, \$7.50.

THE first edition of this excellent book was reviewed in these columns 6 years ago (187, 130, 1934). The new edition is considerably enlarged and every part bears evidence of careful revision. There are a number of entirely new chapters (introduction to normal and pathologic histology of central nervous system, pathology of cerebellum, changes in nervous system due to electrocution). Many new illustrations, particularly microphotographs, have been added. The rapid advances in the field of neuropathology are reflected in the carefully selected bibliography. The book fulfills its purpose: a description of histopathologic changes in their relationship to clinical manifestations.

B. L.

DE MORBIS ARTIFICUM BERNARDINI RAMAZZINI DIATRIBA (Diseases of Workers). The Latin Text of 1713. Revised, with translation and notes by WILMER CAVE WRIGHT, Emeritus Professor of Greek in Bryn Mawr College. Pp. 549. Chicago: The University of Chicago Press, 1940. Price, \$5.00.

THIS bilingual (Latin and English) edition of Ramazzini's great work is one of the best and most important of the History of Medicine Series published under the ægis of the New York Academy of Medicine. It is a worthy successor to Dr. Wright's edition of Fracastorius' *De Contagione*, the second book in this series. Not only does it present for the first time an English translation of Ramazzini's enlarged 1713 edition, but it also includes an enlightening 34-page introduction touching on Ramazzini's life and the medical conditions of the times.

E. K.

LANDMARKS AND SURFACE MARKINGS OF THE HUMAN BODY. By L. BATHE RAWLING, M.B., B.CH. (CANTAB.), F.R.C.S., Consulting Surgeon to St. Bartholomew's Hospital. Pp. 98, 36 illustrations. Eighth Edition (new terminology). New York: Paul B. Hoeber, Inc., 1940. Price, \$3.00.

This is the eighth edition of this little book. Presumably it is intended for surgeons but if the young surgeon needs to study landmarks and surface markings it would probably be well for him to restudy his anatomy. Nothing can take the place of three-dimensional anatomy; but, undoubtedly, if this fact is kept well in mind and the information offered in this book is considered only as an adjunct to the more thorough knowledge, the book may be found of value. The illustrations are clear and, though somewhat too diagrammatic for complete accuracy, should be helpful.

I. R.

THE TREATMENT OF DIABETES MELLITUS. By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., Medical Director, George F. Baker Clinic, New England Deaconess Hospital, etc., HOWARD F. ROOT, M.D., Physician, New England Deaconess Hospital; Consultant in Medicine, Eastern Maine General Hospital, etc., PRISCILLA WHITE, M.D., Physician, New England Deaconess Hospital, etc., and ALEXANDER MARBLE, A.M., M.D., Physician, New England Deaconess Hospital, etc. Pp. 783; illustrated. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, \$7.50.

The seventh edition of this well-known book appears in the form made so familiar by earlier editions, but now under the authorship also of Dr. Joslin's coworkers, Drs. Howard F. Root, Priscilla White and Alexander Marble, who have revised the various sections. A slightly thinner paper has apparently been used so that in spite of a very considerable increase in the number of pages, the book is no larger than the sixth edition.

A new chapter on "Allergy and Diabetes" by Dr. L. Tillman McDaniel has been added. There is an increase of about 75 pages which, with the exception of those devoted to the extra chapter, are distributed largely among those sections in which they could be best used. Coma, cardiovascular and nervous diseases, syphilis and surgery have all received more full treatment. In the chapter on diet 11 pages have been devoted to a review of the present knowledge of the vitamins, especially in their connection with diabetes. There is found the same conservative presentation of recent investigations which have appeared since the previous edition. That these have been brought up to date is evident from the number of references under dates of 1939-1940. These references, very considerable in number, continue not only to show the fundamental basis of the work, but also to act as a very good bibliography of this important field. Numerous tables and graphs aid in the clear presentation of facts.

All in all, this excellent book continues, as heretofore, to be the standard work on diabetes, and should be in the hands of every physician in general practice who desires to be well informed, as well as of those who are working especially in this field.

R. R.

FOOD, NUTRITION and HEALTH. By E. V. MCCOLLUM, Ph.D., Sc.D., and J. ERNESTINE BECKER, M.A., Professor, and Associate, of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University, Baltimore. Pp. 127. Fifth Edition entirely rewritten. Baltimore: By the Authors, 1940. Price, \$1.50.

In the fifth edition of this privately published monograph, the authors have evaluated the recent scientific findings in nutrition in non-technical language for the benefit of the layman.

They discuss the various vitamins, their nature, and the effects of their deficiencies, and continue in the same manner with those mineral elements which are recognized as necessary in promoting normal nutrition. Following the discussion of the dietary properties of foodstuffs both of animal and vegetable origins, the authors take up the relation of diet to various systemic conditions, such as dentition, pregnancy and hygiene of the digestive tract. They discuss diet in relation to weight control and explode some of the various fads which are prevalent today. The variations in the diets of different world areas are explained, and a system of nutrition to promote health is presented in such a manner that the average individual should be able to determine the proper types and amounts of food which should be eaten daily. This chapter is illuminated by many typical diets for the seasons of the year and age of the individuals.

Such a book on account of its simplicity, accuracy and conciseness should fit very well in the present program to interest and explain necessary elements of nutrition as well as the etiology of the deficiency diseases.

P. W.

PRACTICAL HANDBOOK OF THE PATHOLOGY OF THE SKIN. An Introduction to the Histology, Pathology, Bacteriology, and Mycology of the Skin with Special Reference to Technique. By J. M. H. MACLEOD, M.A., M.D., F.R.C.P. (LOND.), Physician and Hon. Director of the Pathological Department, St. John's Hospital for Diseases of the Skin; Physician for Skin Diseases to the Hospital for Tropical Diseases, London, etc., and I. MUENDE, M.B., B.S., B.Sc. (LOND.), Pathologist in Charge of Out-Patients' Clinic and Lecturer in Pathology, St. John's Hospital for Diseases of the Skin; Dermatologist to the Middlesex County Council, Willesden General Hospital, etc. Pp. 415; 125 black and white illustrations and 27 colored. New York: Paul B. Hoeber, Inc., 1940. Price, \$9.00.

This second edition is a marked improvement over the first, both in format and content. Many of the newer developments have been added and, in particular, many new photographic illustrations. Line drawings have practically disappeared. The content is remarkable, considering that the text occupies but 402 pages. Thus, under the general heading of "Pathology" the following sections are included: histologic methods, histopathology, the embryology and anatomy of the skin and its various parts, pigment, bacteriology, mycology, and animal parasites. It is inevitable, however, that under these circumstances much of the treatment is sketchy. Thus, bacteria are covered in 13 pages and pigmentation in 9 pages. One misses a more extensive consideration of the pathologic chemistry in a new book of this sort, the only attempt in this direction appearing in a 5-page chapter on the lipids or fat. Vitamins are not even indexed, even granting that this subject is not yet ripe for the skin. In Chapters 2, 3, 4, 5 and 6, 29 pages are appropriated for the discussion of histologic methods. Such data are available in numerous texts, and the space might have been utilized to advantage for recording additional details concerning other subjects in the book.

The book is well printed, on enameled stock. The illustrations are ample and uniformly good, including the numerous ones in color. There are few typographic errors, but the authors are inconsistent in designating the names of diseases by capital letters in some places, and with lower case in others. In spite of these criticisms, the book is a most welcome addition to the literature of dermatology. It is much needed in America at a time when the specialty is making rapid and long strides in graduate and post-graduate education. To the graduate student in training for the specialty, but also the progressive dermatologist, the book is indispensable.

F. W.

METHODS FOR DIAGNOSTIC BACTERIOLOGY. A Complete Guide for the Isolation and Identification of Pathogenic Bacteria for Medical Bacteriology Laboratories. By ISABELLE G. SCHAUB, A.B., Assistant in Bacteriology, Department of Pathology and Bacteriology, The Johns Hopkins University School of Medicine, and M. KATHLEEN FOLEY, A.B., Bacteriologist in Charge of the Diagnostic Bacteriological Laboratory of the Medical Clinic, The Johns Hopkins Hospital, Baltimore. Pp. 313. St. Louis: The C. V. Mosby Company, 1940. Price, \$3.00.

THE title is a bit misleading in that the statement is made that the book is "a complete guide for the isolation and identification of pathogenic bacteria for medical bacteriology laboratories." Only one side of each page is printed, the other side being left for notes, so the contents of the book is even less than the title and size of the book infer. In reality, the book describes the procedures as carried out in the laboratories of The Johns Hopkins Hospital and School of Medicine. Whether the procedures constitute a "complete guide" or are the best remains for the reader to judge. The information, which is of a practical nature and not readily found in textbooks, represents tests and procedures that are known to be practical.

H. M.

SURGERY OF THE HAND (Wounds, Infections and Closed Traumata). By MARC ISELIN, M.D., Surgeon, The American Hospital, Paris. Translated by T. M. J. d'Offay, M.B., Ch.M. (EDIN.), F.R.C.S. (ENG.), Surgeon and Deputy Medical Superintendent, City General Hospital, Leicester, and THOMAS B. MOUAT, M.D., Ch.M. (EDIN.), F.R.C.S. (ENG.), Surgeon, The Royal Infirmary, Sheffield; Lecturer in Surgery, The University of Sheffield. Pp. 353; 135 illustrations, including 8 plates. Philadelphia: The Blakiston Company, 1940. Price, \$5.50.

THIS, the first English edition of Iselin's work, is a translation of the third French edition, which was published during the past year in 2 volumes. This little volume concerns itself with wounds, foreign bodies and infections of the soft parts of the hand; and fractures, dislocations, and infections of the bones of the hand. There is a short discussion of the social aspects of injuries of the hand and another which briefly attempts to assess the incapacity which follows injury. At the end of each chapter is a short bibliography consisting in the main of French references. This brief account of many common disorders, which all too frequently are mismanaged, is written in a very personal manner so that it is easily read. Where necessary, interesting case reports are included. While it will not take the place of "Kanavel," it will, and rightly should, be a welcome addition to the "Surgery of the Hand."

I. R.

BIOCHEMISTRY FOR MEDICAL STUDENTS. By WILLIAM VEALE THORPE, M.A. (CANTAB.), PH.D. (LOND.), Reader in Chemical Physiology, University of Birmingham. Pp. 464; 37 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, \$4.50.

THIS textbook of biochemistry is divided into three parts. The first part, which deals primarily with the chemistry of solutions and compounds, opens with two chapters devoted to the chemistry of aqueous solutions. These are followed by a discussion of the usual subjects, such as carbohydrates, fats, proteins, and nucleic acid. A short chapter is inserted on animal pigments, then the author takes up enzymes, oxidation and reduction, blood, and the composition of tissues.

The second part deals with body processes and includes digestion, absorption, 8 chapters on intermediary metabolism, including metabolism of the inorganic elements, detoxication, hormones, and vitamins.

The third part discusses energy requirements, nutrition, foods, and excretions. At the end is an appendix containing data concerning the composition of blood, food, excretions, and so forth.

The book is very clearly and well written and covers most subjects quite adequately. There are, however, some omissions which could well have been included in a text at this time. There is, for example, no mention made of either vitamin B₆ or pantothenic acid. Very little is said about vitamin K and none of its chemistry is given. The author has not included a discussion of the uses of isotopes and radioactive substances in connection with intermediary metabolism. The relations of the various enzymes and coenzymes to each other and to the various steps in the transfer of hydrogen to molecular oxygen within the organism could be made more clear.

J. J.

NEW BOOKS.

A Review of the Psychoneuroses at Stockbridge. A Case Study and Statistical Analysis. By GAYLORD P. COON, M.S., M.D., Chief Medical Officer, Boston Psychopathic Hospital, and ALICE F. RAYMOND, A.B., Statistician, Department of Child Hygiene, Harvard School of Public Health. Pp. 299; illustrated. Stockbridge, Mass.: Austen Riggs Foundation, Inc., 1940.

Pathological Conferences held at the Cook County Hospital by Dr. R. H. Jaffé. Edited by CHESTER C. GUY, M.D. Pp. 1164; 1 illustration. Chicago: Cook County Hospital Internes' Alumni Association, 1940. Price, \$3.50, from the Chicago Medical Book Company, Chicago, Illinois.

Los Trastornos Circulatorios de la Avitaminosis B₁. By LEÓN DE SOLDATI. Pp. 364; 35 illustrations. Buenos Aires: "El Ateneo," 1940.

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Man's Greatest Victory over Tuberculosis. By J. ARTHUR MYERS, Ph.D., M.D., F.A.C.P., Professor of Medicine and Preventive Medicine and Public Health, University of Minnesota, and Chief of Medical Staff, Lymanhurst Health Center, Minneapolis. Pp. 419; 31 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$5.00.

Feldchirurgie. Leitfaden für den Sanitätsoffizier der Wehrmacht. Unter Mitwirkung von M. DIETRICH, W. FÖLSCH, Prof. E. GOHRBANDT, H. HARTLEBEN, C. HEINEMANN-GRÜDER, H. KÄFER, G. PANNING, K. PETER, G. SCHÖNEBERG, Prof. O. STAHL, and Prof. H. WILDEGANS (all medical officers of the German army). Herausgegeben von Dr. H. KÄFER, Generaloberstabsarzt. Pp. 354; 58 illustrations. Dresden: Theodor Steinkopff, 1940. Price, Rm. 9.

Bird Malaria. By REDGINAL HEWITT, Sc.D., Department of Protozoölogy, School of Hygiene and Public Health, The Johns Hopkins University. (The American Journal of Hygiene Monographic Series, No. 15, July, 1940.) Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 228; 33 illustrations and 13 plates (1 in color). Baltimore: The Johns Hopkins Press, 1940. Price, \$1.10.

Clinical Roentgenology of the Alimentary Tract. By JACOB BUCKSTEIN, M.D., Visiting Roentgenologist (Alimentary Tract Division), Bellevue Hospital, New York City; Consultant in Gastro-Enterology, Central Islip Hospital. Pp. 652; 525 illustrations. Philadelphia: W. B. Saunders Company, 1940. Price, \$10.00.

Golden Anniversary, 1890-1940, The Waverly Press, Baltimore. Pp. 16; illustrated. Baltimore: The Waverly Press, 1940.

Hydrocephalus. Its Symptomatology, Pathology, Pathogenesis and Treatment. By OTTO MARBURG. Pp. 217; 28 illustrations. New York: Oskar Piest, 1940. Price, \$3.00.

The Medical Clinics of North America, Vol. 24, No. 6 (Philadelphia Number, November, 1940). Pp. 324; 35 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This number contains 8 miscellaneous articles of at least average excellence. They are overshadowed, however, by the 16 articles on the various aspects of rheumatoid disease, a subject that has received special attention in Philadelphia of recent years. Few practitioners will fail to profit from perusal of these up-to-date articles.

Psychiatric Social Work. By LOIS MEREDITH FRENCH, Director, Study of Trends, American Association of Psychiatric Social Workers; Psychiatric Social Worker and Instructor in Mental Hygiene, New Jersey State Teachers College at Newark. Pp. 344. New York: The Commonwealth Fund, 1940. Price, \$2.25.

The 1940 Year Book of Pathology and Immunology. Pathology, edited by HOWARD T. KARSNER, M.D., Professor of Pathology, Director of the Institute of Pathology, Western Reserve University, Cleveland. Immunology, edited by SANFORD B. HOOKER, A.M., M.D., Professor of Immunology, Boston University School of Medicine; Immunologist, Massachusetts Memorial Hospitals. Pp. 688; 115 illustrations. Chicago: The Year Book Publishers, Inc., 1940. Price, \$3.00.

The New International Clinics, Volume IV, New Series Three, 1940. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 17 Collaborators. Pp. 326; illustrated. Philadelphia: J. B. Lippincott Company, 1940.

The 10 original contributions to this number from various parts of the country are on widely different topics (Ewart's sign, convallan, heparin, atypical pneumonia, and so on). The 23 "Clinics," all from the University of Louisville School of Medicine, touch on as many different phases of medical nosology, diagnosis and treatment. C. M. Smyth reviews recent progress in the Management of Spreading Peritonitis of Appendiceal Origin.

NEW EDITIONS.

Developmental Anatomy. A Text-book and Laboratory Manual of Embryology. By LESLIE BRAINERD AREY, Ph.D., Sc.D., LL.D., Robert Laughlin Rea Professor of Anatomy, Northwestern University. Pp. 612; 590 illustrations, some in color. Fourth Edition, revised. Philadelphia: W. B. Saunders Company, 1940. Price, \$6.75.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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GOUT.

IN recent years gout has been termed "the forgotten disease." The disease is out of fashion. But the general awakening of interest in gout which is taking place indicates that it will soon lose this reputation. An editorial in *Lancet*¹⁴ points out that lack of progress in gout is due largely to an absence of intensive study. Inability to reproduce it in animals has helped to discourage research, where prospects of success are meagre. In the sixth rheumatism review of the American and English literature conducted by the American Rheumatism Association,²⁰ about 30 references were available for review. The present report consists of a digest of the recently available literature.

Incidence. Although reports of the frequency and incidence of gout vary considerably, the disease is ever present. English writers⁴⁵ speak of its diminishing incidence, but on the continent, particularly at certain spas, the incidence continues to run about 1 to 2 % of treated patients. Awareness of the possibility of gout is most important in its recognition, and the ease with which it is found when efforts are made to ferret it out bears out this contention. Hill²¹ has shown how changes in hospital staff have influenced the frequency of the diagnosis of gout. Some consider it the most commonly overlooked type of joint disease,²⁶ and statistics at the Cleveland Clinic bear out Hench's contention¹⁹ that about 5 to 8 % of all cases of joint disease in an arthritic clinic are gout. Hench says it is the suspicion of gout and not the disease itself which has disappeared.

The wide variations in the incidence of diagnosed gout may be seen from hospital statistics. Tolstoi⁴⁶ found that in over 177,000 patients admitted to the New York Hospital over a period of 5 years, the diagnosis of gout was made only 8 times. Cohen's figures¹⁰ from the Philadelphia General show 47 diagnoses of gout in 414,000 admissions from 1906 to 1929, an incidence of 1 in 8808. From 1929 to 1935, 30 diagnoses were made in 146,992 admissions, or 1 in 4899; while from January, 1935, to June, 1937, there were 17 such diagnoses in 35,312 admissions, or 1 in 2077.

Age incidence, since the description by Sydenham, has invariably been given as most frequent in middle life. First development of arthritic

symptoms is usually between the ages of 35 and 45, but, of course, the disease sometimes occurs earlier^{21,23,26,32} as well as in more advanced years. More than half of Hill's patients were over 45 years of age. In Kinell and Haden's series the average age of the patients when first seen was 50.5 years; the average duration of symptoms, 7 years, and the age of onset, 33 to 50 years in 60 % of the patients. Vorhaus and Kramer⁴⁷ found 76 % of their patients were first seen in the fifth and sixth decades, but the onset of symptoms occurred in the fourth decade in 56 %. Of 9 females, 78 % developed the disease before the age of 40.

Lambie²⁹ has reviewed the occurrence of gout in children. It is rare but is not unknown at the ages of 6 to 8 years. Attacks have been described in infants at breast.

Reports on sex incidence show striking differences. The usual incidence in women is given as 2 to 3 %. In a recent series²⁶ of 135 patients, 130 (96.3 %) were males and 5 (3.7 %) females. Thomson⁴⁵ states that 10 % is possible in women and that in women the disease is more chronic and atypical than in men, with a greater likelihood of error in diagnosis. Incidence in women has been reported as varying considerably. Such figures as 20 and 36 %^{39,47} are on record. There is, however, no unanimity of opinion as to the validity of the diagnostic criteria²⁰ in the various reports.

Etiology. The cause of gout remains a mystery. A derangement of purine metabolism is acknowledged by all, but its relationship to the cause is obscure. Arguments concerning the place of heredity in gout continue. Such a factor is a time-honored consideration and has been found in some series in from 90 % of the patients down to 1 %. Hill²¹ found a positive family history of gout in 45 %, and of fibrositis in an additional 15 %. He suggests that it may be a transmitted allergic state but finds no abnormal tendency to allergic manifestations in gouty patients and offers no direct evidence for this impression. Heredity appeared to be of little importance in Cohen's cases¹⁰ but his findings do not speak against the possibility as there is great difficulty in obtaining a satisfactory family history from the clientele of a large municipal hospital. Hereditary data from routine clinical records without particular study of the living relatives may be poor.⁴³ Some²³ have found high uric acid levels in relatives of gouty patients, suggesting an hereditary factor. Talbott⁴³ states that diligent medical and social investigation of gouty families discloses evidence which indicates a high familial incidence. This has been true in many older studies quoted by him as well as in his own experiences. In addition he too has found an elevated serum urate in relatives of gouty patients even though the relatives displayed no clinical evidences of gout. This finding occurred in 25 % of 136 relatives from the ages of 14 to over 70 years. That 3 subjects were over 70 years of age indicates, he believes, that an elevated level of uric acid in the body is compatible with good health and a reasonably long life. Again, the constitutional type¹² considered of importance in the development of gout, points to hereditary influences.

Many characteristics of acute gout, such as fever, leukocytosis, increased sedimentation rate, and evidences of inflammation in the joints suggest infection as a cause. There is nothing tangible, however, to support this idea. Infectious processes may initiate joint symptoms but these infections appear to be only precipitating factors, as are lead

poisoning, trauma, operative procedures, certain medications, and blood dyscrasias, some of which, in the past, have been suggested as important primarily in the etiology.

The disease has not yet been linked to the endocrines, although a possible endocrine function of the liver has been thought by some to be perhaps important. Allergy, as stated above, has been suggested as being of etiologic importance because certain dietary factors are known to precipitate attacks.²⁴ Patients have shown eczema, bronchial asthma and urticaria, but there has been no abnormal tendency to allergic manifestations.²¹

Since gout displays a change in uric acid metabolism, and since the liver is concerned to a large extent in uric acid formation, some dysfunction of the liver⁶ has been predicated as being important etiologically. Enlargement of the liver and epigastric symptoms are not infrequent in gout.

The mechanism of hyperuricemia is not established. The general opinion is that it is not the cause but only one of the symptoms of gout.²⁴ Hyperuricemia could result from: 1, increased formation; 2, diminished excretion; or 3, diminished destruction of uric acid. Recent observers favor the first possibility.⁴⁴

Talbott and Coombs⁴⁴ studied the urinary output between and during gouty attacks. They noted 24 to 72 hours before the onset of articular symptoms a diuresis accompanied by an increased excretion as well as increased concentration of various urinary constituents, particularly sodium and chloride. Diuresis continued through the first few days of an attack and the maximum output was usually noted immediately before or on the day of maximum articular distress, when it amounted to twice the daily output prior to diuresis. During diuresis the patients gained weight, presumably because of reduction in insensible loss. These changes were not affected by the weather. The chemical cycles could not be related to temperature and humidity, but a fall in barometric pressure practically always preceded diuresis by 12 hours when there were no articular symptoms and by 12 to 24 hours when acute attacks occurred.

Grabfield's studies¹⁷ on renal innervation suggest an association of the gouty attack with impairment of renal nerve function. Experimental interference with impulses through renal nerves produced effects similar to those observed in gout, for example, greater speed in the excretion of added sodium chloride, initiation of the gouty attack by ergotamine, and diminution of uric acid excretion after ergotamine.

Evidence continues to appear that hyperuricemia does not produce gout through primary renal insufficiency.^{11,21,44} Hill found renal function normal in 9 of 93 patients. Talbott and Coombs⁴⁴ studied renal function in gout and reported patients in whom no renal insufficiency occurred and in whom the kidneys were able to excrete water and solids and to concentrate uric acid satisfactorily. Brøchner-Mortensen⁴ obtained similar results.

In a recent study¹¹ of renal function in gout, function tests included accepted clinical procedures as well as clearance of inulin, creatinine, urate, sodium and chloride. Most of the gouty patients showed some evidence of renal damage; 18 of 27 showed some limitation of renal function. In the absence of severe renal impairment all except 10%

of the urates which were filtered through the glomeruli were reabsorbed by the tubules. Reabsorption was depressed in severe renal impairment. No constitutional inferiority of the kidneys to excrete urates was demonstrated. Cinchophen and salyrgan caused a diminution in tubular reabsorption of urate and an increase in urate clearance. Colchicine did not appear to influence the renal elimination of urates. Kidney changes in patients with gout were believed to be the result and not the cause of the metabolic dyscrasia. Deposition of urates in the kidney parenchyma was seen at postmortem and may be significant in the production of renal deterioration.

Pathology. No attempt will be made here to review the pathologic anatomy of gout. Reports are not numerous, for tissues require special handling. They are not fixed in formalin, which dissolves urates, but are prepared in absolute alcohol and stained with silver nitrate.²⁰ Urate crystals are deposited in cartilage, fibrous capsules to joints and ligaments, tendons, and bursæ, where they provoke a foreign body reaction. Destruction and overgrowth of bone may develop with changes similar to hypertrophic arthritis, and pannus formation similar to that of atrophic arthritis. "Gouty teeth," yellow and worn down, have been interpreted as evidence of gouty constitution, but Gibson and Kersley¹⁵ have seen non-gouty people with them and, of course, gouty people without them. Histologic studies are not helpful.

Bunim and McEwen⁷ have reported an interesting autopsy in which crystals were found and chemical analysis showed the presence of uric acid and the absence of calcium on the mitral valve. The valve showed little if any evidence of previous inflammatory changes. These authors cite previous reports of tophi on heart valves and point out the rarity of such an occurrence.

Clinical Picture. Gout has been described as a chronic disease with arthritic episodes termed "acute explosions."¹⁸ The typical attack of gout has been described so many times that it will not be repeated here. The reader is referred to a recent reprint of Sydenham's classic description.⁴² The attacks are usually nocturnal and may or may not be febrile. Onset may be heralded by such things as a ravenous appetite, or mental reactions of various sorts, but often no symptoms occur.

The obese, florid, pyknic type is most frequently afflicted but not invariably so. Only rarely is the patient a negro.¹⁰ In Kinell and Haden's series²⁶ over 80 % of the patients were obese, 1 patient in 58 being underweight. The plethoric appearance and ruddy complexion was reflected in the red blood count. In 50 % of the patients the red cell count was 4,800,000 or more, and in 24.2 %, 5,000,000 or more. The hemoglobin values corresponded. The authors point out that these values are not striking if compared with those of normal healthy individuals, but when compared with the relatively high incidence of anemia in the clinic and especially in arthritics it is easy to see the origin of the impression of the unusually healthy color of patients with gout.

Certain factors are known to precipitate attacks and many of these have from time to time been suggested as primary causes. Various traumata, sometimes very minor, and surgical operations, which may go in the same category for the present considerations, are predisposing causes. Gout is one of the common types of postoperative arthritis,

especially following genito-urinary surgery, and should be considered in the differential diagnosis of such arthritides. Operations are not always precipitating factors and it is said that some patients seem to be more resistant to an attack in the few weeks following an attack, when operation is better withstood without a flare-up. When flare-up does follow surgical procedures it is usually within 5 days after operation.²⁰

Dietary indiscretions, excessive use of alcohol, and infections, are classical examples of precipitating factors. The foods responsible are not necessarily those rich in purines. Emotional upsets, blood dyscrasias, and various medicinal and chemical agents are also effective in starting attacks. Lead poisoning, especially from drinking water, gold injections, salyrgan, decholin, and thiamin chloride fall into the latter group. Thiamin has been continued under these circumstances and eventually is well tolerated with seemingly beneficial therapeutic value. Vorhaus and Kramer⁴⁷ in 23 (92%) of 25 patients noted a flare-up when thiamin was started. The symptoms started usually in 2 to 4 days and lasted 5 to 10 days. Antisera have been known to precipitate attacks.¹³

Price³⁵ has recently reported further instances of gout following the use of salyrgan for relief of edema of cardiac origin. He observed 5 cases in a period of a little more than a year and suggests that the association cannot be so very uncommon. All patients had a previous history of gout and salyrgan acted as a precipitating factor. The attacks were preceded by periods of diuresis which in 4 of the 5 instances became "critical" 7 to 9 days after salyrgan therapy was instituted. The height of edema fluid and blood uric acid did not appear to be of primary importance in determining the onset of gout. The two factors essential for the appearance of an attack seemed to be a history of gout and a very brisk response to salyrgan. Price also points out that the onset of gout following the use of salyrgan was of grave prognostic significance and brings up the question of the use of mercurial diuretics in patients with a history of gout. Spontaneous gout is preceded by diuresis (*vide supra*) with changes in the excretion of electrolytes. The salyrgan diuresis seemed to parallel it.

Ergotamine is also known to precipitate attacks¹⁷ with diuresis and change in uric acid excretion through neurogenic effects.

Attacks may be precipitated in patients suffering from anemia. Opsahl³⁴ has reported 2 patients with severe anemia, 1 with pernicious anemia, the other with anemia of hemorrhage in whom acute podagra appeared during the period of blood regeneration. The author believes each had a constitutional predisposition to gout and, with regeneration of blood, purines were liberated by nuclear breakdown in the bone marrow, accompanying increased red blood cell formation. He suggests this endogenous uric acid overdosage initiated the attack of gout. In studying the relationship between blood regeneration and endogenous uric acid in a series of severe anemias he found an elevated uric acid elimination with reticulocyte responses. Polyuria occurred with the uric acid increase and reticulocyte crisis.

A relationship between uric acid metabolism and erythropoiesis has been recognized for many years. In 1929 Krafka in this country reported on it. Lambie²⁹ has described gout following blood dyscrasias

and reviewed the literature on its occurrence following such blood diseases as anemia and leukemia, where uric acid production is greatly increased. One would expect a strong proclivity to gout under these circumstances, and, although it does occur, gout is only rarely known following leukemia. Some authors⁴⁰ believe the association is mere chance. Gout may occur as a complication of erythremia as well.⁴ Reifstein³⁷ has reported a female with erythremia, gout, and sub-leukemic myelosis.

Gout has been reported in association with erythromelalgia,³³ with relief lasting 2 years after therapy with typhoid vaccine.

Seasonal variations occur in gouty attacks. Spring is the favored season, autumn less so. In 74 of Hill's 93 cases²¹ a seasonal tendency was noted. As far as sudden changes in weather are concerned, gouty individuals are less sensitive than other arthritics. Only rarely can they forecast storms, and in controlled studies no relationship to temperature or humidity was found.⁴⁴ However, data suggest that barometric pressure changes affect their insensible loss of weight and cause diuresis.

Almost invariably the outstanding clinical findings in the gouty attack are arthritic. The onset is frequently nocturnal. In Hill's group,²¹ 66 of 79 (84%) from whom definite data could be obtained gave a history of nocturnal onset. Theories to explain the onset at night are not satisfactory. They include increased alkalosis, vagotonia at night, and a slowing down of the circulation which might favor the precipitation of urates. The joints become red, hot and swollen, having the appearance of an infection. The typical clinical picture involving the great toe has not changed since the clear description of Sydenham⁴² in the 17th century, and will not be repeated here. Podagra, or involvement of the foot, presumably the great toe, has been considered by many clinicians essential for diagnosis. It may or may not be involved either in the first or in subsequent attacks. In 25% of Kinell and Haden's series²⁶ the original joint affected was another than the great toe. Thomson⁴⁵ found the great toe involved in 60% of males and a lesser percentage of females. Vorhaus and Kramer⁴⁷ found 7 of 25 (28%) with great toe involvement at the onset and state that fully as many had never developed any pains or swelling in the great toe. Multiple joint involvement is very common. Cohen¹⁰ found it in 27 of 41 patients. Almost every joint has been involved, including the temporo-mandibular and sternoclavicular.²⁶ Common involvement aside from the great toe includes the foot, hand, knee, elbow, shoulder and hip, in that order.²¹ Bilateral swelling of the small joints of the fingers with an elevated blood uric acid, relief with colchicine, and complete restoration of function between attacks is very likely gout. The freedom from signs and symptoms between attacks is very important in diagnosis. In the hands finger-spindling may occur, but is not well marked. This may simulate rheumatoid arthritis and sections from the fingers of such patients have shown urate deposits in the joints.

Most observers agree that the chronic stages of gout are preceded by repeated acute attacks with complete remissions between. It may, however, start insidiously and progress without complete remission.^{10,21} The latter is said to occur more frequently in women²¹ where it is likely to affect the small joints of the hands or feet and may be mistaken for

rheumatoid arthritis.⁴⁵ Thomson states, however, that careful inquiry into doubtful cases often elicits transient and trivial attacks which the patient may not mention.

Arthritis is, of course, not the whole picture of gout. The urinary tract may be involved, resulting in chronic nephritis, calculi, and renal insufficiency. Tophi may form and break down. Bursitis occurs. Other manifestations have been ascribed to gout, at times on very doubtful grounds. In the past many gastric, hepatic, and colonic manifestations have been so attributed. Gastro-intestinal findings, including changes in gastric acidity, have been described.³⁶ At times involvement of the iris with nocturnal onset, heat and burning rather than pain, and an accompanying elevation in blood uric acid has been termed gouty iritis.²¹ Palmar and plantar hyperkeratoses,¹ pruritus, eczema and urticaria, neuralgia, myalgia, sciatica, and trigeminal neuralgia accompanied by hyperuricemia and relieved by colchicine and atophan²¹ have been dubbed gouty. Phlebitis, tendinitis, muscle pains, abdominal pains, neuromuscular and nerve tenderness have also been ascribed at times to gout.

Fibrositis was found 14 times as pure gouty disease by Hill,²¹ who also found 21 gouty arthritics with fibrositis. He thinks it is rare, however, for only 15 such were found in 800 to 1200 cases of fibrositis. These patients showed the same etiologic characteristics as typical gout, including a strong family history, predilection for a particular season of the year, initial attack at night, together with a clinical history, course, and biochemical findings expected in gout. Clinically the fibrositis showed the usual muscle tenderness, thickening, nodules, stiffness of the fingers and periarticular swelling. In 8 of the 15 cases, colchicine was tried. In 7 rapid relief occurred. These findings, he feels, make it reasonable to call these cases true gout and not fibrositis in gouty patients.

Tophi are said to be rare in women; some writers do not agree.²¹ They represent a collection of precipitated urate crystals forming a nodule which is most common on the helix of the ear. Other less common locations are the back of the pinna, the olecranon bursa, eyelid, conjunctiva, fingers, and toes.²¹ They may become congested, swollen and red with burning and irritation instead of pain, but often they give rise to no symptoms at all. At times they may break down and ulcerate. When ulcerating they have been mistaken on the heel for pyogenic ulcers.⁹ The frequency of occurrence of tophi has been repeatedly described^{4,21,44,47} in up to 58% of the patients. The incidence in the references cited is 23, 33, 43, and 58%, and depends, among other things, upon the stage of the disease. In the chronic stages they are more easily found. However, they may occur at any stage or not at all and have been absent after 40 years of known gout.²⁷ Their occurrence does not correlate with the level of blood uric acid.

Tophi prove the presence of gout so that without them the disease is called pretophaceous or presumptive, and with them, tophaceous or proved gout. More will be said of this under *Diagnosis*, below.

Roentgen Ray Examination is of little value early⁴⁵ when the joints may show no abnormality by this method of examination. As the disease progresses more positive diagnoses are expected. A variety of non-specific changes has been described. Vorhaus and Kramer⁴⁷ found

abnormalities in bone detail in 24 of 25 patients. Kinell and Haden²⁶ had positive Roentgen ray evidence in 19 cases (30.6%). The examination is regarded as helpful but not final and the help comes chiefly in those instances when the diagnosis is obvious on other grounds. Thomson⁴⁵ states that although larger joints are involved it is best to rely on the hands and feet for Roentgen ray evidence of gout.

Typical findings are eroded areas at or near joints. Such "punched out" areas are characteristic and the radiologic diagnosis is described as often simple.¹⁶ However, they do not prove gout^{4,24} for they may simulate closely bone cysts and certain changes of rheumatoid and hypertrophic arthritis. They are most significant when large. Kienböck²⁵ feels that Roentgen ray examination is important in the differential diagnosis of gout and painful nodules of the digits due to tuberculosis.

Laboratory Data. Much of this has been given above. Anemia, as stated under *Clinical Picture*, is usually not present. The leukocyte count may be elevated, particularly in the attack, with an increase in neutrophils and a shift to the left. Statements³⁹ that gout is incompatible with an alkaline urine do not fit with the fact that such instances have been found.²⁰

The sedimentation rate is elevated in the acute attack and returns to normal rapidly with recovery.²¹ In Kinell and Haden's²⁶ group, 85% of 62 cases showed an elevation which varied with the clinical activity of the disease. Correction of infections did not bring the rate to normal. The exact cause for the change in the sedimentation rate is not known. The usual explanation is that of changes in plasma fibrinogen which in gout have been vaguely ascribed to toxic substances or faulty liver function. Several groups of observers^{21,26,39} have found no correlation of the blood uric acid and the sedimentation rate.

Hyperuricemia occurs in a vast majority of patients at some stage of their disease.^{4,19-21,23,26,43,44,47} Since a great number of techniques for this determination are in use, interpretation of the level depends upon a knowledge of the normal standards for each. Some²³ believe that collection of blood under oil is important. One has the choice of using whole blood or serum, preferably the latter. For whole blood the technique advocated by Jacobson (Folin, 1933) gave a mean value of 4.2 mg. per 100 cc. in non-gouty individuals. In 97 individuals the serum uric acid was less than 6 mg. per 100 cc.

In acute attacks uric acid levels are usually elevated, but this is not necessarily so. Since attacks of acute arthritis may occur without hyperuricemia, the diagnosis is compatible with normal values and must sometimes be made in their presence. Between attacks the values are frequently normal. It must be remembered, as already stated under *Etiology*, that members of gouty families may have elevated uric acid levels for long periods of time without any other evidences at all of gout.^{23,43} Late in the disease the values are usually high between attacks and in chronic gout the same is true. Tophi are said to occur only rarely without hyperuricemia.

By itself elevation of the blood uric acid is not adequate for diagnosis. Gibson and Kersley¹⁵ found it in 2% of 251 undoubted atrophic arthritics and 5.4% of 184 other rheumatic states.

Other data on uric acid have been given elsewhere in this review.

Diagnosis. Diagnosis rests to a large extent upon awareness of the possibility of gout and is not difficult if the basic clinical picture is kept in mind.²⁶ Sudden involvement of a single joint, whether it be in the great toe or not, should lead one to think of gout. Polyarthritides as well, coming on in attacks and leaving the patient entirely free between attacks, is most important; hence the great value of a complete history. Some³² consider an adequate history describing the characteristic features of a single attack with complete remissions between them as the most important single diagnostic feature.

The type of patient susceptible to gout has already been discussed. Onset of pain is sudden and severe, first involving a single joint which becomes swollen, red and tender. Early attacks last a few days to 2 weeks and subside gradually. Attacks may recur after symptom-free intervals and may be precipitated by the factors already given. As time goes on attacks may last longer and finally may result in chronic disease with joint deformities.²⁶ The importance of differential diagnosis lies in the entirely different management, treatment and prognosis of gout compared to other joint diseases. Important in the differentiation in the acute stages are rheumatic fever, gonococcal arthritis, traumatic joints, acute bursitis, hemophilia, acute rheumatoid arthritis, and septic joints.³² That the inclusion of gout in the differential diagnosis of these and similar states is not routine in the minds of many physicians is shown in the long period intervening between the first attack and the diagnosis of gout. These statistics have already been given. As another example, Vorhaus and Kramer⁴⁷ found this period in their patients to average 8.8 years.

Laboratory evidences have already been given above, particularly uric acid and Roentgen ray studies. The importance of the tophus has also been discussed. Tophi should be recognized as such only after the presence of sodium biurate crystals has been demonstrated in them. Since laboratory data are not always helpful, clinical diagnosis is very important, and may have to be carried to the point of using a therapeutic test. Such tests, as relief with cinchophen or with purine-free diets, are not sufficiently specific to be unquestioned.²⁰ The reaction to colchicine is the most promising procedure (see the use of colchicine under *Treatment*, below).

Variable results have been obtained by use of provocative tests, especially the high purine diet.⁴ Gibson and Kersley¹⁵ have found provocative tests inconclusive. Delayed uric acid excretion on high purine diets is not diagnostic for it has occurred in atrophic arthritis. Thiamin has provoked attacks⁴⁷ but its value as such a test is not yet established. Ketogenic diets have also been used in borderline cases. Lockie³¹ and others⁴ have not found such high fat diets always successful, but the former precipitated attacks in 9 of 10 experiments with a low carbohydrate, low protein, high fat diet.

Prognosis. The hereditary nature of the metabolic defect in gout indicates that the gouty tendency will persist until death. As in diabetes mellitus there are methods of control but none of cure. Some³² doubt if anything materially affects the course of the disease. General opinion, however,⁴⁴ is that much may be done for the patient, especially in controlling the frequency and severity of attacks and in administering symptomatic relief.

Complications. Many of the so-called complications of gout have been considered as part of the disease itself. These have been discussed under *Clinical Aspects* and *Pathology*. Renal stones and gravel due to urates are frequent. Talbott and Coombs⁴⁴ found urate stones in 24 of their patients and renal colic preceded the symptoms of arthritis in 2. Renal stones of similar nature occur in individuals without gout, but certainly should initiate a thorough examination of the patient for gout.²⁰

Chronic nephritis with renal insufficiency is not uncommon. Impaired renal function is common in gout.^{11,21,44} Schnitker and Richter³⁸ found vascular nephritis in 31 % of 55 patients. The finding of urate deposits in the kidneys indicates that at times the renal damage may result directly from the disease. However, arteriosclerosis and hypertension are very common.

Glycosuria has been described in gouty patients. Hill²¹ found none in his 93 patients. French statistics show an incidence of less than 1 %, but it is said to be more common in Germany. Umber had 15 diabetics in 278 instances of gout. However, in Germany there is no unanimity of opinion and some believe the association is mere chance.⁴⁰

Treatment. No striking advances in the treatment of gout have appeared recently and reports continue to reiterate the value of the standard forms of therapy. There is no known cure and the gouty tendency persists until death. Treatment of attacks¹⁰ includes bed rest, fluids, hot compresses locally, low purine diet, colchicine and symptomatic care. Saline or mercurial purges at the onset of and during attacks are time honored.

Dietary restrictions apply to calories for control of obesity as well as for elimination of purine containing foods;^{22,45} chiefly beans, peas, fowl, meat, fish, and gravies and other meat extracts.²² Alcohol is forbidden. In certain patients other foods, for example cider, have been important and required elimination.⁶ Studies of the effects of a low purine diet on uricemia have given variable results²³ but its use for long periods of time is a well established part of treatment, even though alone it is not an effective form of therapy as judged by changes in serum uric acid.

Bartels² emphasizes the fact that much stress has been placed on treatment of the acute arthritic manifestations and little on their prevention. Purine restriction, as well as other dietary restrictions, has been part of the therapy of gout between attacks as well. Bartels points out the use of high carbohydrate-low fat diet by others and proposes the high carbohydrate-low fat-low purine diet along with other forms of therapy. In 4 cases the use of this procedure resulted in no further attacks of joint pains and the blood uric acid returned to a normal level.

Colchicum has proved its effectiveness in acute attacks in report after report. It may be given as the wine, 15 to 30 minims every 3 to 6 hours, or as colchicine in 1/100 to 1/120 grain doses. The latter preparation is given according to various schemes. The stated dose may be given every 1 to 3 hours until diarrhea develops or until arthritic symptoms are controlled. It relieves the acute symptoms readily and is often given as a therapeutic test. Lockie³¹ gave 1/60 grain doses for 24 to 72 hours until diarrhea developed, when it was discontinued. In 75 gouty patients he obtained marked relief, while in a miscellaneous group of 50 arthritics he did not. Bowers³ gives 1/100 grain 6 to 8

times daily for 2 to 3 days. Talbott and Coombs,⁴⁴ who regard colchicine as probably the most important gout drug, use similar dosage, 1/120 grain every 1 to 2 hours for 8 to 16 doses, depending on tolerance and severity of attack. Ludwig, Bennett and Bauer³² also regard colchicine practically as a specific. They give 1/120 grain every 1 to 2 hours until nausea, vomiting and diarrhea develop and then discontinue it. Paregoric may be necessary to control the diarrhea. They find that freedom from pain and subsidence of swelling occur within 24 to 72 hours. After the amount for toxic symptoms has once been established, they reduce the dose by 1 to 2 tablets and still get the desired effect. Additional therapy includes avoidance of precipitating factors, a high fluid intake, and 60 to 80 grains of aspirin 4 days out of every week. The mechanism of the action of colchicine is not known. Recent studies³⁰ of its effect on malignant tissues apparently do not explain its action in gout.

Cinchophen is not used universally³² and some advocate estimations of liver function before it is tried. Some¹⁰ use it only where idiosyncrasy to colchicine exists. It was introduced early in the 20th century and used extensively because of the uric acid excretion produced. Salicylates have a similar but less marked effect, and have been used where cinchophen is contraindicated. The mode of action is unknown. Grabfield¹⁷ suggests from studies in man that the site of action of cinchophen may be in the nervous system and it is possible that the normal stimulus to uric acid excretion is neurogenic.

Bryce⁵ found 190 cases of cinchophen poisoning in reviewing this subject. The patients over 40 years of age were more susceptible. Females were more likely to develop it than males and expectation of recovery was greater in males than in females. These compounds are consumed in large quantities, thousands of pounds yearly, and reported instances indicate that toxicity is rare in terms of the amounts used. All cases, however, are not reported. Patients may not develop symptoms with its use at first and may not experience a toxic reaction until later on. Sugg⁴¹ found 26 such patients in the literature and added 6 of his own. The mechanism of reactions to cinchophen is not known.

A recent addition to the therapy of gout is thiamin chloride. Vorhaus and Kramer⁴⁷ have utilized it in 1 to 10 mg. doses (330 to 3300 I.U.) daily. As stated elsewhere in this review, a flare-up of symptoms occurred in 23 of 25 patients (92%) in the first 2 to 4 days. In spite of this the vitamin was continued and no reactions recurred. In 1 to 3 years of treatment moderate or marked relief was obtained in 12 patients. The authors feel that it will take a longer time really to evaluate this therapy. Kühnau, Schroeder and Wolff²⁸ also report promising results. Callahan and Ingham⁸ utilized doses from 4500 to 9000 I.U. daily, with cinchophen, 0.5 gm. 4 times a day, and a purine-free diet combined with balneotherapy. They feel that this regimen greatly reduced the period of disability. Vorhaus and Kramer conclude only that their observations justify continued study as an experimental therapeutic agent and that further observations are necessary to clarify the relationship between gout and thiamin.

Interval treatment to prevent attacks has been discussed above. It is the subject of much argument and many outlines of treatment have been utilized. Without the indices of relief such as pain in the acute

attack, Talbott and Coombs⁴⁴ believe the number of attacks per year is the best index of effectiveness of therapy. Colchicine for 1 week out of 4, or for 2 to 3 days per week has been advocated.

Spa treatment is considered helpful by some in the chronic stages⁴⁵ but not in the acute attack.

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PEDIATRICS.

UNDER THE CHARGE OF

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THE VITAMINS AND THEIR DEFICIENCIES WITH SPECIAL REFERENCE TO CHILDHOOD.

ACCORDING to Garrison⁹ it was Frederick Gowland Hopkins who was earliest to recognize the significance of vitamins in his observation that a diet lacking in amino acids, arginine and histidine, or composed of

only 5 simple amino acids of the 18 composing protein, will fail to maintain life. That lack of certain elements in the dietary was responsible for the development of typical clinical pictures was known for many years is evidenced by the fact that ships' crews were provided with lime juice to prevent scurvy and that cod-liver oil was given to babies to prevent certain bone changes. The knowledge of these deficiencies was entirely empirical. Identification of definite factors and their specific properties occurred within the professional life of many who are still comparatively young. So much enthusiasm was engendered by the results of the application of the new knowledge that the literature became replete with reports and studies. As is so often the case this seemed a good field for commercial exploitation and vitamins have been produced for sale in department stores and groceries. In spite of this the true value of these products in the medical armamentarium has not been lost, but because of further scientific developments in this field they have become more firmly entrenched. The literature is filled with references on this subject. Some of the most recent of these have been used as the basis of this presentation of the subject.

Avitaminosis A may manifest itself in four principal ways. These consist of eye lesions such as nyctalopia or night blindness, xerophthalmia and keratomalacia; dermatoses such as keratosis, abnormal dryness or scaliness and loss of hair; susceptibility to infection, and retarded growth. In addition to these, dental changes and urinary calculi have been blamed upon inadequate vitamin A. Lehman and Rapaport¹⁹ found that the dermal lesions of their patients were symmetrical and located chiefly on the extremities, and more particularly on the lower extremities. The lesions are composed of, horny papules formed by keratotic plugs projecting from hair follicles and frequently containing a broken off hair or a coiled unerupted hair. Although these cases had no eye symptoms, in every one the readings of the biophotometer were definitely in the subnormal zone, indicating a vitamin A deficiency. The authors gave a therapeutic test in some cases. This consisted of taking a biophotometric reading and then administering 200,000 international units of vitamin A by mouth. Subsequent tests made 1 and 2 hours later indicated some improvement in the biophotometric reading by a rise from the deficient to the borderline or normal zone.

Clausen and McCoord⁴ reported studies that call attention to the more important factors which affect the level of the carotenoids and of vitamin A in the blood, such as placental transmission, diet, infection, age and season and the effect of certain morbid states such as diabetes, Bright's disease, celiac disease and hypothyroidism. Large amounts of carotene and xanthophyll may pass through the placenta to the fetus. Vitamin A probably also passes through the placenta, but the fetus may be able to form vitamin A from carotene. Normal infants and older persons readily absorb carotene from the diet, but the rate of absorption is slower than the rate of absorption of Vitamin A. The low carotenoid content of the diet in early infancy and in the winter months explains the lower concentration and xanthophyll in the first 6 months of life and in the winter. The mean plasma concentration of vitamin A in normal persons reaches a constant level soon after birth and is not affected by season. Infection, partly because of low

intake and partly because of fever, causes a prompt fall in the concentration of carotene, xanthophyll and vitamin A in the plasma. The vitamin A content of the plasma may rise above the normal a few days after the temperature becomes normal. In severe untreated cases of diabetes the tissues may not be able to metabolize carotene rapidly. In nephrosis and severe chronic nephritis, hypercarotenemia may occur without xanthosis cutis, which in normal persons, in diabetic persons and in persons with hypothyroidism is associated with an increase of carotene in the plasma and less often of xanthophyll. In Bright's disease the vitamin A level of the plasma may be partly elevated, probably because the liver fails to store it. In hypothyroidism the carotenoids of the plasma may be elevated and vitamin A may be low. Treatment with thyroid substance corrects this. In celiac disease the carotenoids and vitamin A are readily absorbed.

May *et al.*²³ described a photoelectric colorimeter technique, using selective light filters, for the quantitative estimation of vitamin A and the carotenoids in small amounts of serum. With this technique the rapidly changing blue color may be read instantly at its maximum; subjective error is eliminated; selective light filters allow for correction due to blue color arising from the carotenoids; carotenoids and vitamin A may be determined with the same aliquot of extract; the small amounts of color obtainable from 1 cc. of blood serum may be measured accurately, and the entire procedure is simple to perform. Its accuracy and dependability were indicated by the results obtained when duplicate analyses for carotenoids and vitamin A were done on separate specimens of the same blood. By means of this technique normal well-nourished children from birth to 12 years of age were found to have levels of vitamin A in their blood ranging from 5.5 to 27.3 units. The level of carotenoids also covered the wide range from 3.1 to 75.7 units. The wide range of values was not confusing, as the alterations in the levels of vitamin A and carotenoids in pathologic states were beyond the limits seen under normal circumstances. In acute infections with fever, the blood levels of both vitamin A and the carotenoids decrease. The levels may rise spontaneously to normal during the subsidence of the infection. As the bodily stores of vitamin A are depleted the carotenoids in the blood decrease, and not until these have been considerably lowered does the level of vitamin A begin to fall. In some of the infants, whose intake of vitamin A and carotenoids was restricted, the levels in the blood dropped considerably below the lowest limits of normal. The low levels in the blood were the only clue to a deficiency of vitamin A and dropped before the appearance of cornified epithelial cells in the conjunctiva and respiratory and genito-urinary tracts. These studies indicate that the vitamin A customarily supplied to infants in ordinary whole cow's milk formulas may be scarcely sufficient to maintain an optimal level of vitamin A in the blood. If the absorption of vitamin A from the intestine is impaired, depletion of the bodily stores and lowering of the level on the blood may be expected, even when the vitamin A intake is normal. Their study of intestinal absorption was facilitated by utilization of the vitamin A absorption test of Chesney and McCoord. Failure of the level to rise to normal after ingestion of vitamin A, in the form of 0.1 cc. of percomorph liver oil per pound of body weight, may be assumed to indicate a decrease in

intestinal absorption. Impaired intestinal absorption has been found in congenital obliteration of the bile ducts, fibrosis of the pancreas, celiac disease and cretinism, where the average rise was 8.2 units after absorption test doses, as compared to 129.7 units in normal children. There was no advantage in parenteral administration of the vitamin, but the defect in absorption may be easily overcome by the oral administration of unusually large amounts of vitamin A, preferably in divided doses. The presence of a low absorption curve was an indication for the administration of large amounts of vitamin A in order to maintain normal levels and prevent deficiency.

Friderichen and With⁷ studied the quantity of carotenoids and vitamin A in breast milk. They found that the content of vitamin A and carotenoid in mother's milk undergoes considerable variation from day to day. This variation does not run parallel to the fat content of the milk. If the diet was sufficient with regards to vitamin A content, content of vitamin A and of carotenoid in mother's milk gave no variation for winter or summer, although occasionally fairly great variations independent of diet and season occurred. After peroral administration of carotene an increase of the serum carotene was observed but no increase in the content of vitamin A and of carotenoid. The diet, of which the nursing mother receives about 75 international units per kilogram of body weight per day, is not only sufficient as regards vitamin A but is actually optimal. If the diet is sufficient, the administration of vitamin A preparations during lactation is superfluous.

The cow's milk content of carotene and vitamin was studied by Dornbush, Peterson and Olson.⁵ Their observations were monthly over a period of 18 months. The commercial milks fall into four groups: market, which is mainly Holstein; Guernsey; vitamin D, which is mainly Holstein, and certified milk. All milks showed seasonal changes in both carotene and vitamin A contents. The seasonal changes in carotene were greater than those for vitamin A. The milks were fairly similar in vitamin potency per gram of butter fat. Certified milks were somewhat higher than the other milks during the late winter months. Guernsey milk, because of its higher fat content, had a higher potency on the fluid basis than the others. Per quart the winter milks from January to April averaged: market, 327 micrograms, or 1088 U.S.P. units; Guernsey, 372 micrograms, or 1241 U.S.P. units; and certified, 400 micrograms, or 1334 U.S.P. units. For summer milks from June to October the figures were: market milk, 572 micrograms, or 1906 U.S.P. units; Guernsey, 727 micrograms, or 2415 U.S.P. units; and certified milks, 599 micrograms, or 1995 U.S.P. units.

The question of the requirements of the body for vitamin A has been the subject of considerable study. It had been held that the average diet of artificially-fed infants contained an adequate amount of vitamin A. This was based on the fact that no improvement in the nutritional status or increase in the immunity to infection was brought about when large quantities of vitamin A in the form of cod-liver oil or halibut oil were added to the average diets of infants. In infants receiving only one-fourth of the vitamin A content of the average diet there was no difference in the nutritional state or the resistance to infection. This gave rise to some question as to the need for some more sensitive criterion. As night blindness is conceded to be a very early

manifestation of vitamin A deficiency, preceding retardation of growth, susceptibility to infections and xerophthalmia, Lewis and Haig²¹ devised an apparatus and developed a technique by means of which night blindness or dark adaptation could be estimated even in children less than 1 year of age. They reported their observations of the minimum light threshold after complete dark adaptation on 53 infants ranging in age from 1½ to 13 months. These infants were divided into four groups: Group 1 consisted of 26 infants receiving the average infants' diet; Group 2 consisted of 9 infants receiving a diet supplemented by large quantities of vitamin A (17,000 units) in the form of halibut-liver oil; Group 3 consisted of 4 infants receiving a diet containing approximately one-fourth the vitamin A content of the average diet; and Group 4 consisted of 14 infants receiving about one-twelfth the vitamin A content of the average diet. These diets were given for periods varying from 3 to 10 months. The results of the dark adaptation tests were within normal limits in all four groups of infants. Those in the low vitamin A group gained weight just as well and were no more susceptible to infection than those in the high vitamin A group. These observations indicated that 135 to 200 units of vitamin A, or approximately 25 units per kilogram of body weight, covered the minimum vitamin A requirements of these infants. Since the average diet contains 12 times as many units of vitamin A as were contained in the low vitamin A diet used in this study, it is apparent that there is a large margin of safety in the infant's diet in respect to its vitamin A content and it would seem unnecessary to supplement this element in the average diet of infants.

Although there is the above-cited latitude in vitamin A requirements of normal children, Breese and McCoord^{3a} reported a series of cases of celiac disease, which showed a subnormal absorption of vitamin A. Even when given a large amount of vitamin A by mouth these patients did not show an increase in the blood vitamin A content equal to that of a group of children with other diseases. This inability of the patient with celiac disease to absorb vitamin A was usually associated with a flat sugar tolerance curve, increased per cent of fat in the stools and low carotenoid pigments in the blood. This inability to absorb vitamin A normally, although characteristic of celiac disease, does occur in other diseases and therefore is not pathognomonic of celiac disease.

In another communication^{3b} the same authors reported their studies of vitamin A absorption in 21 patients with catarrhal jaundice. The first vitamin A absorption test was normal for 6, while in the remaining children either the vitamin was absorbed poorly or the rise in the blood was found to be much higher than normal. The icteric index did not bear any obvious relation to vitamin A absorption. Severe degrees of hepatic damage, as measured by the bromsulphalein test, were associated in 3 cases with failure to absorb vitamin A, whereas lesser degrees of damage were not. Patients with low curves, who were given bile salts and retested, showed improvement in absorption. This improvement was maintained in most cases when the test was repeated without the use of bile salts.

An interesting study of the effects of avitaminosis A on the blood picture was made by Ahmann and Overstreet¹ on a group who had been living on restricted diets for periods that varied from a few months

to many years. The children had lost the alertness of health and were listless and inattentive, but conjunctivitis was the most outstanding defect of this group. In a few cases the ocular condition had progressed so far that there was actual involvement of the cornea and the conjunctiva appeared salty. The skin had become dry and desquamated. These flaky areas were particularly noticeable on the back of the forearm, the upper part of the arm near the tips of the shoulder, on the calves and across the chest. Many of the children had no subcutaneous fat, so that the skin on the face was shriveled and dry. The hair was also dry, had lost its normal gloss and appeared bleached and lifeless. A study made of the differential leukocyte counts of 157 subjects whose diets and symptoms indicated a deficiency of vitamin A. The characteristic changes, which were constant in the blood pictures of these subjects, were mild leukopenia, a decrease in the number of neutrophils, a relative increase in the number of large lymphocytes with a corresponding drop in that of small lymphocytes, the occurrence of degenerated cells and an increase in the number of immature cells. From these findings it is shown that the differential leukocyte count is of value in diagnosing the deficiency of vitamin A in man.

Vitamin B is a complex which is composed of some six individual factors. According to Goodman¹¹ the most important are vitamin B₁ and B₂, or as it is often designated B₂ (G). Vitamin B₁ is called the antineuritic vitamin. The richest source of this vitamin is yeast. The wheat germ and the outer husks of cereal grain are rich in vitamin B₁ as are also egg yolk, milk, vegetables, especially the leaves, citrus and other fruits, and meat. Vitamin B₁ promotes growth, reproduction and lactation. A slight deficit causes disturbance of the alimentary tract. This in turn leads to indigestion, loss of appetite, retarded growth and weight and to intestinal upsets. Severe lack of vitamin B₁ causes beriberi in humans and polyneuritis in fowls. Vitamin B₂ was originally thought to be a single substance, but is now known to be made up of several factors. Vitamin B₂ is generally regarded as the growth-promoting vitamin, and to consist of a number of antidermatitis factors and the P-P or pellagra-preventive factor. Lack of B₂ (G) results in changes in ocular tissue with formation of cataract; loss of hair, ulceration of the tongue and, in certain combination of circumstances, in pellagra.

Price²⁷ pointed out that adequate amounts of vitamins are recognized as being essential to health and the B group is thought to be one most likely to be supplied in sufficient amount in infancy. Vitamins A, C and D are prescribed for most bottle-fed babies but of vitamin B the infant receives only the small amount present in the milk formula and to a small degree from the orange juice which is given for its vitamin C content. Breast milk has been shown to contain even less vitamin B₁ than cow's milk, so that there may develop evidences of vitamin B₁ deficiencies in both breast- and bottle-fed infants. Vitamin B₁ increases muscle tone and is thought to correct anorexia and constipation through this action. Carbohydrate metabolism is dependent on the presence of vitamin B₁ for its completion of the oxidation process. The vitamin is thought to act as a catalyst. In deficiency states the lactic acid produced by muscular activity accumulates and is very slowly oxidized and removed. In this way there is developed fatigue, atony and

possibly the accumulation of toxic end-products of metabolism. This vitamin also plays some essential part in the well-being of lymphoid tissue, as deficiency leads to lymphoid atrophy.

In discussing the relation of vitamin B deficiency to infant mortality, Sure³² stated that, of all the disturbances responsible for infant mortality during the first year, none caused greater apprehension than diarrhea and enteritis because 20% to 30% of infants die of gastro-intestinal diseases of vague etiology. Because the maternal diet and the artificial feeding of infants can never be controlled completely and rigidly, particularly from the standpoint of depleting vitamin reserves, there is a great likelihood of these gastro-intestinal disturbances being the result of vitamin deficiency. The author found that the nursing young of the albino rat required 11 times as much vitamin B in the form of dehydrated yeast as vitamins A and D in the form of cod-liver oil in order to maintain continuous growth during the nursing period. Although beriberi in an accentuated form is seldom encountered in this country in the human baby, a large proportion of the infant mortality during the first year of life which is associated with gastro-intestinal disturbances may be due to vitamin B deficiencies.

Albert² called attention to a disease which prevails in the Philippine Islands and endangers the life of nurslings during the early months of life. He found that it plays an important rôle in infant mortality and strangely was found to be more severe in breast-fed infants than in artificially nourished ones. He described three clinical forms: the aphonic, the pseudomeningitic and the cardiac. The last named is the most interesting, as well as being the most serious, form. Clinically there is very acute cardiac failure associated with dyspnea, cyanosis and pallor appearing in stout, fat, well-developed infants, who are otherwise normal. There is restlessness with incessant crying, resembling congenital syphilis. The weakness of the heart is associated with gallop rhythm, accentuation of the second pulmonic sound, smallness of the pulse and enlargement of the heart. In most cases the onset is abrupt without any prodromal symptoms except inconstant vomiting. The mother usually believes that her baby is in excellent health. Death may ensue very early after the onset. The age period of its occurrence is between the first and the third months and it usually is found in infants nourished by mothers with latent beriberi. It often happens that the mothers succumb after the death of their babies.

The influence of the vitamin B complex on growth and constipation was studied by Joslin and Helms.¹⁵ Their findings indicated a definitely increased growth in infants in length, in development of the chest and in weight as the result of an increased amount of vitamin B given in the diet during the first year of life. Constipation was relieved in each instance of the 35% of this series which manifested the symptom. In their control group the 20% who manifested constipation did not show a disappearance of this symptom upon the use of the usual laxatives such as mineral oil, milk of magnesia and the like. In another group of nursing infants who had failed to gain in weight because of insufficient breast milk, vitamin B was added to the diet of the mothers. Of these, 57% were able to continue nursing their babies for periods varying from 2 to 6 months. Of this group of infants 50% were constipated. The addition of the vitamin B to the diets of the mothers cleared up all

but 5% of these cases. In 100 older children it was found that 27 had anorexia while 40 were constipated. These were all fed a proper diet and given a special cereal rich in vitamin B. The appetite in each case was improved and the constipation was corrected.

In studying 800 pellagrins in the Nutrition Clinic of the Hillman Hospital in Birmingham, Ala., Spies, Walker and Woods³¹ extended the study to include the families of these patients. A diagnosis of pellagra was made in 194 children and 6 infants, and in each case the diagnosis was confirmed by therapeutic tests. Although their studies were not completed at the time of the report, certain points concerning the manifestations of pellagra in infancy and early childhood were clarified. They examined the children of pellagrous parents repeatedly, with particular attention directed toward the diet of the mother during pregnancy and lactation and of the child after birth, towards the physical and mental development of the child, and towards the presence or absence of lesions diagnostic of pellagra. It was often found that the diet of the mother was inadequate during pregnancy and lactation and that, as a result, the quality of her breast milk was poor and the supply often insufficient for the child's needs so that the nursing infant had to be weaned soon after birth and was given some sort of food, which in many cases was inadequate for its nutritional needs. As they grew older, the majority of these children had poor appetites and usually ate very irregularly. Most of them preferred carbohydrate foods and often refused most of the other foods. Analysis of the dietaries of such children showed that in most cases their diets were unbalanced and failed to supply in adequate amounts the foods essential for proper nutrition. Usually these children were underweight and underdeveloped for their age and appeared to be undernourished and in ill-health. They were said to be irritable, easily frightened and fretful and cried a great deal. They were listless, tired and apprehensive and they did not manifest the normal interests of childhood. Those of school age found it difficult to concentrate and, as a rule, made poor progress in school. Although they seemed too tired to play, they could not rest. They did not sleep well at night but instead tossed about and frequently awoke crying. Many of them complained of soreness of the tongue and lips and of burning and pain in the stomach. Usually they suffered from constipation but they might have attacks of diarrhea during the spring and summer. The response to antipellagic treatment was as dramatic as it is in adults. The administration of nicotinic acid or yeast was followed by rapid improvement and it was also observed that similar improvement followed the use of the monocarboxylic and dicarboxylic acids of pyrazine. Lesions characteristic of the disease were seldom seen in infancy but frequently appeared early in childhood. In the absence of typical symptoms the administration of one of the therapeutic agents specific for pellagra offers a valuable therapeutic test in confirming a diagnosis of latent pellagra.

The development of knowledge concerning the vitamins includes striking examples of the application of the results of experimental investigation to clinical medicine, as is brought out by a recent Editorial in the *Journal of the American Medical Association*.⁶ The point was well illustrated by our present knowledge of the vitamins of the B group, which is sometimes called the vitamin B complex. Early it was demon-

strated that this factor had profound effects on growth, gastro-intestinal motility, appetite, carbohydrate metabolism, integration of nerve action and other physiologic processes and functions. These observations led to a search for the individual substances composing the B group. The chemical nature of B₁ and of B₂, or G, has now been established and confirmed by synthesis, as also has been the structure of the antipellagric substance, nicotinic acid, which is also a member of the B complex. To the vitamins of the B group which are known in chemically pure form and in synthetic form, namely thiamin or B₁, riboflavin or B₂ or G and nicotinic acid, the factor B₆ must be added. At least six B vitamins have been proposed and other factors with a variety of nomenclatures have also been proposed for inclusion in the B group of vitamins. There is some uniformity of opinion in the use of the term vitamin B₆ which has been applied to that factor of the B complex which prevents or cures acrodynia-like dermatitis in young rats. It has also been stated that puppies on a vitamin B₆ deficient diet develop a severe microcytic hypochromic anemia, which is cured by the addition of this factor to the diet. The structure of vitamin B₆ has been recently established and a complete synthesis of the vitamin has been reported as conclusive support of the proposed structure. One of the interesting developments in the chemistry of vitamin B₆ is the demonstration that the substance is a derivative of the nitrogenous base pyridine, being a methyl, hydroxyl, dihydroxymethyl substituted pyridine. The importance of the pyridine nucleus already established in biologic oxidation and reduction appears to indicate that certain functions of vitamin B may be concerned with similar types of biologic reactions. Striking improvement in muscular and neurologic symptoms followed the use of vitamin B₆.

Recognition of the results of vitamin C deficiency is of historic age, although knowledge of the definite causative factor is of more recent origin. That the citric fruits protected against the disease was learned when the condition broke out in the long voyages that were necessary in sailing ships before the advent of more rapid marine transportation. The recognition of scurvy as a frequent cause of distressful conditions in infants and young children is a development within the professional life of many of us. The use of the Roentgen ray to aid in the definite diagnosis of this condition was considered a great contribution within the last 20 years. It is now possible to determine the vitamin C content of the blood, of the spinal fluid and of the urine. By the use of these estimations Wortis, Liebmann and Wortis³⁸ found that no specific level of vitamin C at any given moment in the blood, spinal fluid or urinary excretion was necessarily associated with the clinical manifestations of scurvy. They gave by intravenous injection 1 gm. test dose of cevitic acid (ascorbic) acid to 133 patients. They found that a blood content of vitamin C above 0.7 mg. per 100 cc. was almost invariably associated with a normal spinal fluid content and a normal urinary excretion test for vitamin C. A blood content of vitamin C below 0.4 mg. per 100 cc. was almost invariably associated with a subnormal spinal fluid content and a subnormal urinary excretion test. In these ranges the blood was an accurate index of the state of the vitamin C nutrition. In the intermediate subnormal range for blood of from 0.4 mg. to 1.69 mg. per 100 cc. all available tests should be used, includ-

ing the clinical evaluation of the patient. While these tests are of value and interest, diagnosis of scurvy cannot be made from the tests alone because scurvy is a clinical entity.

Snelling and Jackson³⁰ measured the ascorbic acid content of the plasma of pregnant women. They found a slight fall toward the end of pregnancy. In addition, factors associated with labor lower the ascorbic acid in the maternal blood. The fetus acts as a parasite and has higher levels than the antepartum maternal blood. Totally breast-fed infants were found to be well supplied with vitamin C if the ascorbic acid of the breast milk was greater than 4 mg. per 100 cc.; but if the ascorbic acid level was below 2 mg. per 100 cc. there was a likelihood of a deficiency state developing in the infant. In artificially-fed infants not receiving additional vitamin C, the level of acid in the blood was low. They recommended that artificially-fed infants receive additional vitamin C from the time that they are 2 weeks old. The mothers of breast-fed babies should have adequate vitamin C in their diet and if there is any question of the lack of vitamin C in her diet, the infant should receive additional vitamin C.

The excretion of cevitic acid in the urine and the concentration of this acid in the blood were studied by Ingalls¹⁴ in 7 infants who were proved to have scurvy. Absolute depletion of cevitic acid in the urine and lowering of the levels in the plasma from 0.15 to 0 mg. per 100 cc. were found. Increase in the cevitic acid in the urine and elevation of the levels in the plasma depended on the dose of cevitic acid employed in the treatment. The greater the dose the more rapid the replenishment of the vitamin. These results suggested that there are zones in the excretion of cevitic acid in the urine which are generally characteristic of frank scurvy, of asymptomatic scurvy and of suboptimal and of optimal intake of vitamin C. It appeared that recovery from frank scurvy depended on the quantitative replenishment of cevitic acid in the tissues through stages of absolute and then relative depletion until an adequate depot had been attained.

Hamil *et al.*¹² studied a large group of infants in an effort to determine the minimal vitamin C requirements. From the data that they gathered by means of the finer criteria for diagnosis it appeared that the condition that has usually been considered as latent scurvy is actually definite mild scurvy. Such a distinction puts an entirely different interpretation on the evaluation and classification of symptoms and causes of scurvy. It seems that scurvy is a definite pathologic entity but does not become evident or retard development until the absence of the specific physiologic functions of the vitamin is manifest. A condition of chronic mild scurvy may exist for several months, with spontaneous clearing and recurrence accompanied by its resultant retarding effects on cellular function and physiologic processes of tissues. The symptoms of severe manifest scurvy, comprising the classic entity of Barlow's disease, develop through a combination of factors, which include continued low utilization of vitamin C and diminished cellular metabolism in interrelated functions of the tissues as a result of infection, allergy or glandular heritage. There is a distinct variability in individual susceptibility which is determined by prenatal as well as postnatal factors.

Overstreet²⁶ was impressed by the increase in the number of cases of

scurvy that came under his attention in the hospital. This increase was difficult to explain on the basis of poverty as most of the families were receiving an ample diet. It is his opinion that the disease is not one of poverty so much as one of ignorance. While the vitamin C is present in varying amounts in cow's milk, it is a fragile substance and is largely destroyed by pasteurization or evaporation. He attempted to correct the avitaminosis by the administration of vitamin C specifically. In these infants there were usually other deficiencies in food intake as well as the anorexia which is so greatly a part of the disease. It was necessary to give a well-balanced diet as regards all accepted food elements, including minerals and fluids. Cod-liver oil was given to insure a proper amount of vitamins A and D. Vitamin B aids in improving the appetite. Vitamin C can be administered in the form of orange juice under most circumstances. Ascorbic acid can be given parenterally as well as by mouth. The prognosis in scurvy is almost uniformly good, both as regards life and deformities.

A very interesting study was made by Lever and Talbott²⁰ for the purpose of confirming or rejecting the presumption that a deficiency of vitamin C in the body was a contributory etiologic factor in the production of certain diseases of the skin. Because some observers had reported low level of vitamin C in the blood or a diminished excretion in the urine of patients with certain skin diseases and improvement under treatment with large amounts of vitamin C, the question arose as to the rôle played by this vitamin in such skin conditions. The vitamin C content in the blood of 68 apparently healthy persons and of 181 patients with various skin diseases was determined. The healthy group ate their meals in an institution where a balanced diet relatively rich in vitamin C was served. While some did not care particularly for fruit, others enjoyed it a great deal and complemented their daily intake from outside sources. In this group the level of vitamin C in the plasma ranged from 0.1 to 1.46 mg. per 100 cc. with an average of 0.6 mg. per 100 cc. It was noted that those with low levels ate fruit only occasionally. The skin diseases included psoriasis, urticaria, lupus vulgaris, lupus erythematosus, atopic eczema, exfoliative dermatitis, purpura, pemphigus, acne vulgaris and some miscellaneous lesions. This group showed an average vitamin C blood concentration of 0.36 mg. per 100 cc. The three diseases in which the lower concentrations were especially noted were purpura, exfoliative dermatitis and pemphigus. As a result of their study the authors were unable to find a direct correlation between the level of vitamin C in the blood and the various skin diseases.

Vitamin C deficiency may play a part in the etiology of certain infectious diseases such as acute rheumatic fever. Rinehart²⁸ studied a group of patients including their dietary histories, assay of their social environment, capillary resistance tests, routine examinations and periodic follow-up. It was found that most of these rheumatic children were on the borderline of nutritional inadequacy. Many were severely deficient in vitamin C intake particularly during the winter months. In many instances the economic status precluded adequate food. In other instances racial habits or idiosyncrasies led to a low consumption of foods containing vitamin C. The capillary resistance tests revealed in general low levels particularly in those cases manifesting

evidence of recent rheumatic activity. Many children were found to have edematous, puffy gums. The patients were instructed to provide generous amounts of vitamin C in the diet. Usually a definite daily dietary of orange juice was prescribed. Altogether there was satisfactory increase in the weight, general clinical improvement and absence of recurrence. The levels of capillary resistance rose.

In other infectious diseases vitamin C has been thought to be of some value as a therapeutic agent. Szirmai³³ investigated the value of this vitamin in treating toxic diphtheria, in typhoid and in pneumonia. In toxic diphtheria with edema of the mucous membranes the death rate was greatly reduced when, in addition to the large doses of serum, ascorbic acid was given. As a rule, 300 mg. of ascorbic acid was administered intravenously, simultaneously with the serum, but in a separate syringe so as not to impair the antitoxin. When intravenous injection was technically impossible, the acid was given intramuscularly. The parenteral administration of 300 mg. of ascorbic acid was repeated daily for from 3 to 4 days. In addition the patients were given from 50 to 100 mg. of ascorbic acid by mouth 3 times a day for about a week. In mild typhoid the patients were given the juice of 2 or 3 lemons daily. Patients with typhoid of moderate severity were given in addition 100 mg. of ascorbic acid by mouth 3 times daily. Patients with typhoid in severe form were given daily intravenous doses of 300 mg. for from 4 to 5 days. Under this management intestinal hemorrhages were almost completely prevented. In diphtheria and in typhoid favorable results were obtained even when the doses were not sufficient to produce saturation. In pneumonia the deficit of vitamin C had to be completely compensated before therapeutic results were noted. Children with lobar pneumonia were given intravenous injections of 300 mg. of ascorbic acid once or twice daily. It was emphasized that from 2000 to 3000 mg. per day is necessary to produce saturation in pneumonia patients.

Hemorrhage in some form is often present in avitaminosis C. This may fit the clinical picture of what has been called the hemorrhagic diathesis. Winckelmann³⁷ stated that these conditions must all be treated with large doses of vitamin C until the organism is completely saturated. This is indicated by an excess elimination of reducing substances in the urine. The deficit is usually so large that the 100 mg. of ascorbic acid which represent the customary daily dose are of little effect. In hemorrhagic diathesis deficits of as much as 34,000 mg. are not rare. In thrombopenia it is especially necessary to give large doses so that saturation may be accomplished quickly. The author contended that vitamin C, even in its artificial form of ascorbic acid, was not a dosable medicament. It must be used only with the idea of balancing the deficit which is existing. In order to determine the deficit 300 mg. of ascorbic acid are given the patient by mouth in divided doses over the forenoons. In the afternoon, always at the same hour, the amount of reducing substances present in the urine is determined. After several days if the average readings are exceeded, the deficit has been covered. In hemorrhagic diathesis this effect is rarely produced in less than 8 days of overloading administration and sometimes it takes 15 days or more. In the healthy or in individuals absorbing a fair amount of vitamins with their food, it appears on the

first or second day. The doses, which are necessary to maintain a balanced budget of vitamin C fluctuate around 100 mg. per day, depending on the chronicity of the disease, the quality of the diet and the physical condition of the patient. In conditions where the effect must be produced rapidly, larger doses must be used and given intravenously. Even after a few hours if the reducing substance in the urine is still below 10 mg. per 100 cc., the dose must be renewed and this done daily until the elimination is at least 10 mg. per 100 cc. Also for the maintenance of the saturation, doses up to 400 mg. may be required. Pneumonia and hemorrhagic diathesis are the diseases that require the largest doses.

An interesting study of vitamin C in epilepsy was presented by Merritt and Foster.²⁴ In discussing the effect of dilantin sodium on vitamin C balance they pointed out that the vitamin C content of the plasma of apparently healthy persons on a well-balanced diet was usually between 0.8 and 1.2 mg. per 100 cc. The results of determinations, on large numbers of individuals with no signs of scurvy, showed a variation over a much wider range so that it should be said that the vitamin C content of the plasma of an individual represents the relative dietary intake of vitamin C during the preceding few weeks. Because of the fact that foods rich in vitamin C are relatively expensive, it is not surprising that the vitamin C content of the plasma of patients in the low economic group or in institutions for the care of the mentally or chronically ill is much lower than that usually considered as normal. They found that the plasma vitamin C content of 257 ambulatory patients with convulsive seizures varied between 0 and 1.6 mg., with an average of 0.45 mg. per 100 cc. The plasma vitamin C content of these patients was in no way influenced by the type of therapy that they received. The long-continued administration of dilantin sodium had no effect on the vitamin C level of the plasma and did not influence the absorption of vitamin C given orally. Hypertrophic gingivitis, which developed in patients under treatment with dilantin sodium, was not related to the vitamin C content of the plasma nor to the utilization of vitamin C. That the low level of vitamin C in the plasma of these clinic patients with epilepsy was due to an inadequate intake of this element was proved because administration of food with an adequate vitamin C content resulted in an increase to 5 times the original readings.

Vitamin D has been long the subject of much study and of many contributions to the literature. Although its use as a prophylactic accessory to the dietary of infants is widespread, many papers are published relative to the effects of its lack, of its use or of its relationship to other phases of the human organism. Heymann¹³ studied the antirachitic efficacy of vitamin D in rachitic rats in which obstructive biliary cirrhosis had been induced by ligation and transection of the common bile duct or in which the liver had been damaged by administration of carbon tetrachloride. Further, it was desired to learn whether the impairment of the antirachitic potency of vitamin D observed under these conditions was due to the damage itself or whether it must be attributed to other circumstances accompanying the experimental conditions. To cure rickets in rats in which biliary cirrhosis had been produced, 10 to 12 times as much vitamin D was needed,

in the form of viosterol or of drisdol given intramuscularly, as was required in rachitic rats without biliary cirrhosis. The antirachitic efficacy of parenterally administered solutions of sodium glycerophosphate was not diminished in rats with obstructive biliary cirrhosis, which showed that jaundice did not lead to impairment of osteogenetic cells. To cure rickets in rats in which hepatic damage had been effected by the administration of carbon tetrachloride 2 to 3 times as much vitamin D, given as viosterol in oil by intramuscular injection, was needed as in rachitic rats which did not receive carbon tetrachloride. These studies showed that the impairment in hepatic function resulting from biliary atresia or hepatic damage was responsible for the decreased antirachitic effect of vitamin and consequently the liver plays an important part in the antirachitic functioning of vitamin D.

Meyer²⁵ stressed the fact that the principal rachitogenic factors are artificial feeding and scarcity of light. He felt that the protective vitamin D originates in the body of the child under the influence of ultraviolet rays, therefore specific prophylaxis and treatment of rickets may be achieved by irradiation. Vitamin D is recommended for use also, especially a form containing pure crystalline vitamin D₂ in an oil. While there are advantages of simplicity and low cost, the disadvantages are possible toxic effects resulting from excessive doses. Vitamin products should always be administered under medical supervision as the permanent use of vitamin D in non-rachitic children may be serious. When cod-liver oil is used, only standardized preparations should be employed both for prophylactic and therapeutic purposes. Tetany was found usually in association with rickets. The inorganic phosphorus is diminished in uncomplicated rickets and the calcium content is either normal or slightly below normal, while in tetany the inorganic phosphorus in the serum is either normal or increased and the calcium is diminished.

Gill¹⁰ remarked that since the recognition of avitaminosis D as the paramount factor in the production of true rickets, certain rare cases have been described, where the administration of the vitamin in whatever manner or dosage failed to produce that healing of the disease which regularly occurs in the vast majority of cases of rickets. These cases show clinically and radiologically the picture of florid rickets, and the differentiation from the common nutritional type can only be made from the lack of response of this type to therapy. Even enormous doses produce little or no effect upon the condition and the lesion is cleared up only when growth ceases. Four such cases were observed, in none of which was there any evidence of malnutrition, lack of sunlight, calcium drain, celiac or renal disease. Likewise in none of these cases did any of the known forms of therapy given over a period of several years produce any evidence of healing. It is difficult to understand the mechanism of the production of these cases of vitamin-resistant rickets. In nutritional rickets and in rickets due to lack of sunlight, the response to therapy is invariably rapid and striking. In celiac disease the etiology of the rickets is fairly well understood and ultraviolet light alone causes healing. In advanced renal disease there is gross impairment of renal function with a consequent profound disturbance of calcium and phosphorus metabolism and alteration of their balance. In this group of cases not only was the renal function

normal, but the figures for blood calcium and blood phosphorus remained within normal limits. On the other hand, the blood phosphatase was invariably high, as it always is in active rickets, giving some indication of the activity of the rachitic process. Since vitamin-resistant rickets is evidently not due to nutritional disturbances, lack of sunshine, hyperparathyroidism, faulty absorption or renal impairment, and since the condition heals spontaneously when growth ceases, it was thought that the fault may be a failure of utilization at the site of bone growth.

From 89 complete bioassays of human blood serum an average vitamin D content of 116 U.S.P. units per 100 cc. was calculated by Warkany and Mabon.³⁶ When the results of all of the valid line tests obtained in this study were considered, an average vitamin D level of 110 U.S.P. units per 100 cc. was calculated. Cod-liver oil is the substance that is most frequently tested for its vitamin D content. Although the oils from the livers of individual cod fish may show enormous variations, the average vitamin D content of medicinal cod-liver oil may be rated as 10,000 to 15,000 U.S.P. units per 100 gm. From this it is seen that human blood serum has approximately one-hundredth the potency of medicinal cod-liver oil. The yolk of hens' eggs has been reported to contain in February and June 140 U.S.P. units and 390 U.S.P. units per 100 gm. respectively. Thus the average vitamin D content of egg yolk would be twice that of human serum. Butter with a vitamin D content of 120 U.S.P. units per 100 gm. has an anti-rachitic potency equal to that of human blood serum. Mammalian liver is reported to contain from 10 to 50 U.S.P. units per 100 gm. which is a rather small amount as compared to human blood serum. The level of vitamin D in cow's milk varies from 0.5 to 4 U.S.P. units per 100 cc. according to the season. Human milk apparently contains no appreciable amount of vitamin D. Human blood serum had the highest vitamin D content of all the mammalian material examined so far.

According to the usual therapeutic procedure the time employed in the administration of vitamin D covers weeks or months. Discussing the use of one massive dose of vitamin D in the treatment of rickets and tetany, Vollmer^{35b} called attention to the question that his previous publication has provoked discussion of the toxicity of such dosages. He pointed out that the fear that vitamin D possessed toxic properties dated back to the reports of pathologic calcification following the use of the old German preparation, vigantol. This was evidently very toxic. He showed the harmlessness of one single dose of 600,000 units of vitamin D theoretically, and practically demonstrated this by its administration to 158 children in whom no toxic manifestations occurred. It is therefore recommended for certain clinical purposes. The absorption of vitamin D depots can be accelerated by using a mixture of oil and ether instead of oil alone as solvent. Rickets and tetany responded to this form of parenteral vitamin D shock therapy as promptly as to the oral administration of equal doses of vitamin D. Serum calcium and phosphorus became normal usually after 3 to 7 days. Roentgenographic evidence of calcification showed within 1 week, and recalcification is usually complete 30 days after beginning treatment. Tetanic convulsions ceased within 24 hours after the parenteral administration of one massive dose of vitamin D. Vollmer's original com-

munication^{35a} on this type of therapy was based on observations reported on experimental animals in 1928.

Zelson³⁹ employed this method of administering vitamin D in 46 premature infants as a prophylactic measure. Of 17 who could be followed for from 44 to 279 days, no rickets appeared in those who had received 600,000 units of vitamin D₂ or D₃ parenterally. There was one premature infant who received 500,000 units of an oral vitamin D preparation on the twenty-first day of life, who showed rickets at the beginning of the fourth month. A second dose of 600,000 units of vitamin D₂ parenterally cured the rickets and prevented recurrence up to 262 days of age.

Another use for vitamin D was presented by Knapp,¹⁷ who advocated its use in keratoconus. This condition, he quoted Graves as defining, is a hyperbolic bulging of the central part, or whole, of the cornea with thinning of the center and not accompanied by inflammation or increased tension. All of the patients treated with viosterol and mineral mixture tablets improved subjectively and objectively. His work included observations on experimental animals in addition to the clinical cases. From a consideration of this material he suggested that the calcium-phosphorus metabolism is an important factor in the development of the cornea. It would seem that the lack or deficiency of these metabolic factors would favor weakness of the membrane. This weakness may manifest itself as a primary, non-inflammatory ectasia of the cornea. The administration of vitamin D and calcium gave such encouraging results that it was thought that the etiologic factor of this perplexing pathologic entity had been demonstrated.

Vitamin E is not directly used in pediatric therapy. Gaedke and Bennholdt-Thomsen⁸ discussed its influence on the lactation of mothers and the influence on the growth of their children. They indicated that this vitamin may influence the glands of internal secretion and also the metabolism of iron and manganese. Usually excess of vitamin is excreted and its presence in breast milk has been demonstrated. In this study the quantity of milk secreted and the fat content were not increased. Even when the quantity of the milk varied the amount of fat secreted remained the same. It was found that the influence of vitamin E supplements on the increments in weight and length was negative, but this negative result should not be interpreted as indicating a lack of effect of vitamin E on lactation and on the growth of the infants but rather that the diet was adequate in vitamin E.

Many contributions on the subject of vitamin K are seen. Shettles, Delfs and Hellman²⁹ reported that the plasma prothrombin of the newborn infant can be significantly raised by feeding vitamin K concentrate to mothers either for a prolonged period prior to delivery or during labor. The same result, but to a lesser degree, can be obtained by the feeding of vitamin K directly to the newborn infant. When it is considered that 20 to 40% of neonatal deaths are associated with cerebral hemorrhage and that the low plasma prothrombin level may be a factor in these hemorrhages, vitamin K should be a definite therapeutic need.

MacPherson, McCallum and Haultain²² found that the administration of vitamin K, either to the mother between 12 and 4 hours before delivery or to the newborn, would be especially indicated in cases of maternal toxemia; in premature labor; in cases of difficult or instru-

mental delivery; where breast feeding is not possible; where any cerebral symptoms develop during the first few days of life; in cases of hemorrhagic diathesis, icterus gravis neonatorum and anemia, and where an operation is necessary on the newborn.

Kugelmass¹⁸ stated that vitamin K is an essential in human nutrition for the maintenance of normal blood clotting function. It is involved in the synthesis of prothrombin and is directly related to the concentration of the latter in the circulation. While vitamin K is a valuable adjuvant in the treatment of latent or active hemorrhagic disease of the newborn, he urged that therapy should not be limited to a precursor of prothrombin when the active substance can be injected into the circulation in the form of a blood transfusion. He felt that there was no indication for the use of vitamin K routinely to protect the newborn from possible hemorrhagic disease because there is ample prothrombin for clotting shed blood. Abnormally high prothrombin content cannot prevent blood from oozing through a damaged vascular system unless the entire circulation is clotted. The contention that the prevention of hemorrhagic disease of the newborn will necessarily diminish intracranial hemorrhage is only partially true, because the former is a disease of the blood and the latter a result of trauma to the vascular system. A normal blood coagulability does not preclude vascular injury and *vice versa*.

Kato and Poncher¹⁶ observed in their study that the most important clinical finding is the fact that the average newborn infant possesses a smaller fraction of prothrombin complement than an adult. They felt that this explains in a most satisfactory manner the exact pathogenesis of hemorrhagic disease of the newborn, which is clinically known as melenae neonatorum. In this condition the chief manifestation is frank hemorrhage from the mucous membranes of the gastro-intestinal tract, genito-urinary surfaces and from the umbilical stump. In many of the cases that were observed with this disorder the blood prothrombin was usually demonstrated to be below 10% of the normal adult complement. This gave a greatly prolonged clotting time or none at all. In certain cases of intracranial hemorrhage occurring at birth, trauma or difficult labor may play only a provocative rôle and the fundamental factor is reduced prothrombin convertibility of the blood. Their observations emphasized the great importance and desirability of determining the prothrombin clotting time of every newborn infant or if this is not possible adequate prophylactic measures should be instituted before the infant is born.

Tocantins³⁴ stated that the human newborn infant has a hypoprothrombinemia in a moderate degree at birth, in greater degree between the second and the sixth day of life and gradually diminishing degree during the first 12 months of life. The reason for this is not clear but it has been attributed to a possible dietetic deficiency in the mother although plasma prothrombin values in the mother at term are usually higher than normal. Because of its early appearance it cannot be due to food deficiency in the child. Another possible cause has been suggested in the lack of a well-developed bacterial flora in the intestine of the newborn. He stated that the so-called physiologic icterus of the newborn results from the fact that an excessive amount of bilirubin derived from hemolysis of erythrocytes is delivered for excretion to a

liver with a subnormal excretory capacity. It is perhaps during this interval when a condition of hyperbilirubinemia is making great demands on a defective bilirubin excretory mechanism, that a period of hepatic insufficiency more pronounced than that already present in the newborn supervenes, as well as further impairment in the formation of prothrombin. The functional and structural immaturity of the liver of the newborn probably accounts for the fact that a prothrombin deficiency appears relatively early, after a short period of incapacity, as compared to the time of its appearance in the adult.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION-OF NOVEMBER 19, 1940

The Production of Glycosuria in the Normal Rat by Means of Stilbestrol. DWIGHT J. INGLE (The George S. Cox Medical Research Institute, University of Pennsylvania). It was observed that the administration of stilbestrol to partially depancreatized male rats uni-

formly increased the severity of the diabetic state. The experiments were extended to normal male rats (body weights approximately 300 gm.) which were maintained on a high-carbohydrate diet administered by stomach tube twice daily. The total available carbohydrate of the diet was 15.5 gm. per day. When stilbestrol was administered a glycosuria was induced in 23 of 31 animals studied. The largest amount of glucose excreted in any 24-hour period was 20% of the total available carbohydrate of the diet. The latent period between the beginning of the administration of stilbestrol and the beginning of glycosuria was 1 to 10 days. Although treatment was continued the glycosuria disappeared after being continually present for periods of 2 to 36 days. During the periods of glycosuria the values for blood sugar were .250% to .350% following feeding, in contrast to the normal tolerance to the diet observed prior to treatment. The mechanism of the diabetogenic activity of stilbestrol is not known. It is the first substance found to be capable of inducing a prolonged hyperglycemia and glycosuria in the normal rat. The amounts sufficient for the intensification of the glycosuria of the partially depancreatized rat are smaller with stilbestrol than with the pituitary extracts and adrenal steroids studied in this laboratory.

The Anticonvulsive Action of Mercurial Diuretics. R. BEUTNER, J. P. LANDAY and A. LIEBERMAN, Jr. (Hahnemann Medical College). Previously published experiments from this laboratory demonstrated the prevention of procaine convulsions by suitably large additions of organic or inorganic Ca-salts. We now find that the convulsions from strychnine, picrotoxin or other convulsants can be prevented in the same way. Searching for the pharmacologic mechanism of this *local* action we now believe that tissue dehydration, leading to tissue diuresis, was the important factor. This was corroborated through experiments with diuretics such as salyrgan, mercurin, and novasurol, as follows: salyrgan, or another mercurial diuretic, was added to a solution of a convulsant and injected intramuscularly in guinea pigs. Convulsions from various convulsants were thus prevented. Salyrgan is far more "anticonvulsive" than any calcium salt studied so far since only 20 mg. are necessary to prevent convulsions from 200 mg. of procaine which otherwise is invariably convulsive and oftentimes fatal. This action of salyrgan *cannot be renal* since it does not occur if salyrgan is injected before the convulsant (even though a simultaneous renal action was demonstrated by other methods). A direct chemical interaction of salyrgan and the various convulsants seems unlikely because of their widely divergent chemical character. One might possibly assume a chemical combination between alkaloids like strychnine, or the basic procaine, and salyrgan; but, how can a convulsive glucoside like picrotoxin ever combine with salyrgan? Positive evidence against the existence of a chemical combination was found when we performed similar experiments on frogs. Here salyrgan proved to have no effect upon strychnine convulsions. Strychnine (0.002 mg. per kg.) was found to be invariably convulsant to frogs. Salyrgan (0.1 to 0.01 mg. per kg.) was added to it before the injection, with no perceptible effect. Obviously, salyrgan should inhibit strychnine convulsions in frogs as well as in guinea pigs if a chemical combination is the reason for this

inhibition, but this is not the case. It seems that in the loose tissue of the frog, strychnine has a direct access to the nerve cells, whereas in the muscle of warm-blooded animals the tissues are rendered more impermeable by salyrgan. Xanthin diuretics were found to have *no* anticonvulsive effect pointing to an exclusively renal action.

Peripheral Circulatory Failure in Diabetic Acidosis. A. E. SCHECTER, B. H. WIESEL and C. COHN (Metabolic Division and Laboratories of the Philadelphia General Hospital). A clinical picture similar to that seen in "surgical shock" is frequently associated with severe diabetic acidosis. The present studies were made to ascertain the presence of physiologic changes which might account for this clinical picture.

Eight patients with diabetic acidosis admitted to the Metabolic Wards of the Philadelphia General Hospital on the services of Drs. E. S. Dillon and A. J. Sindoni, Jr., were studied. Temperature, pulse rate, respiratory rate and blood pressure were recorded every half hour. Blood sugar and CO₂ combining power of plasma were measured every 3 hours. Serum proteins, cell volume by hematocrit and hemoglobin were studied. Peripheral blood flow was measured by the hand plethysmograph and recorded during treatment. Arterial and venous blood samples were drawn without stasis from the femoral vessels. Oxygen content, oxygen capacity and CO₂ content were determined.

Serum protein, hematocrit and hemoglobin values were elevated above normal, suggesting hemoconcentration. Peripheral blood flow was reduced in all cases, with most marked reductions in the most seriously ill patients. Blood pressure was reduced in the same group. All patients had a rapid pulse rate. Blood gas analyses showed normal arterial blood oxygen saturation. Venous oxygen saturation ranged from 83.3% to 89% in 5 cases, was 63.8% and 64.2% in 2 cases, and 45.2% in 1 case.

The rapid pulse rate, low blood pressure, markedly reduced peripheral blood flow and hemoconcentration fit into our present conception of the physiologic changes associated with peripheral circulatory failure. However, a high venous oxygen saturation was found in the presence of a markedly reduced peripheral blood flow. This is in contradistinction to the low venous oxygen saturation usually associated with markedly reduced peripheral blood flow in peripheral circulatory failure.

The physiologic evidence presented supports the clinical impression of the existence of peripheral circulatory failure in diabetic acidosis. The existence of a high venous oxygen saturation in the presence of a reduced peripheral blood flow suggests a failure of oxygen utilization by the tissues. These findings point to the existence of a histotoxic as well as a stagnant anoxia in the peripheral circulatory failure of diabetic acidosis.

Types of Orthostatic Hypotension and Their Treatment. WILLIAM A. JEFFERS, HUGH MONTGOMERY and ALAN C. BURTON (Edward B. Robinette Foundation, the Eldridge Reeves Johnson Foundation for Medical Physics, and the Medical Clinic, Hospital of the University of Pennsylvania). The physiology of adaptation to the erect position is reviewed as the basis for an understanding of orthostatic hypotension.

The most important facts are peripheral vasomotor activity, and changes in heart rate.

This is a clinical study of normal subjects, of patients following surgical sympathectomy, and of patients with orthostatic hypotension. Deductions are based upon the behavior of the blood pressure, pulse rate, digital blood flow and skin temperature. According to their reactions to the tests above, patients are classified as having orthostatic hypotension due to slight or marked impairment of reflex vasomotor function, or to mechanical defects in the circulatory system.

A rationale of treatment is presented. Favorable results were obtained by the simultaneous use of benzedrine and paredrinol.

The Effect of Pregnancy Upon Experimental Hypertension in the Rabbit. JOHN D. CORBIT, Jr. (Department of Obstetrics and Gynecology, University of Pennsylvania). The effect of pregnancy upon blood pressure, blood urea, urinary excretion of protein, and body weight, was studied in 5 rabbits in which chronic arterial hypertension had previously been produced by the operative method of Pickering and Prinzmetal. A similar study was made in a control group of 5 normal animals, and in a further control group of 11 animals in which the operative procedures had been carried out, but in which only a temporary hypertension had resulted, or in which no elevation of blood pressure had occurred prior to the mating of the animals.

The changes produced by pregnancy were the same in all groups, and were as follows: A conspicuous fall of blood pressure and blood urea occurred just before the end of pregnancy, and persisted throughout the first 2 weeks of the postpartum period. Proteinuria was common during the same period. The extent of these changes was apparently conditioned by the number of fetuses carried *in utero*.

The results indicate that gestation does not cause an aggravation of renal-ischemic hypertension in the rabbit.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

FEBRUARY, 1941

ORIGINAL ARTICLES.

BLOOD PRESSURE DETERMINATIONS BY PATIENTS WITH
ESSENTIAL HYPERTENSION:

II. THE DIFFERENCE BETWEEN HOME AND CLINIC READINGS
DURING AND AFTER TREATMENT.*

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IN an earlier paper^{1a} it was shown that the blood pressure in untreated patients with essential hypertension is often considerably lower in the home than in the office or clinic. Consequently it was decided to re-evaluate the effects of the common forms of therapy by recording blood pressure measurements obtained during therapy in the home as well as in the clinic. In the present discussion the need for and the advantages of this approach in evaluating therapy will be emphasized; detailed results in each of a large number of different forms of treatment will be presented in the subsequent communications.

Material and Methods. The responses to therapy of all of 34 hypertensive patients previously described were studied, using the same method of home and clinic blood pressure study. In all cases the clinic blood pressure was well above 160 systolic and 100 diastolic, the renal function was good, and there was no evidence of heart failure. The ocular fundi showed moderate to marked narrowing of the arterioles in all, with, in addition, choking of the discs in 2 instances.

In 13 of the 34 cases the blood pressure was taken by the patients themselves, while in the remaining 21 the blood pressure was taken by some member of the household. It is essential to stress again the fact that the

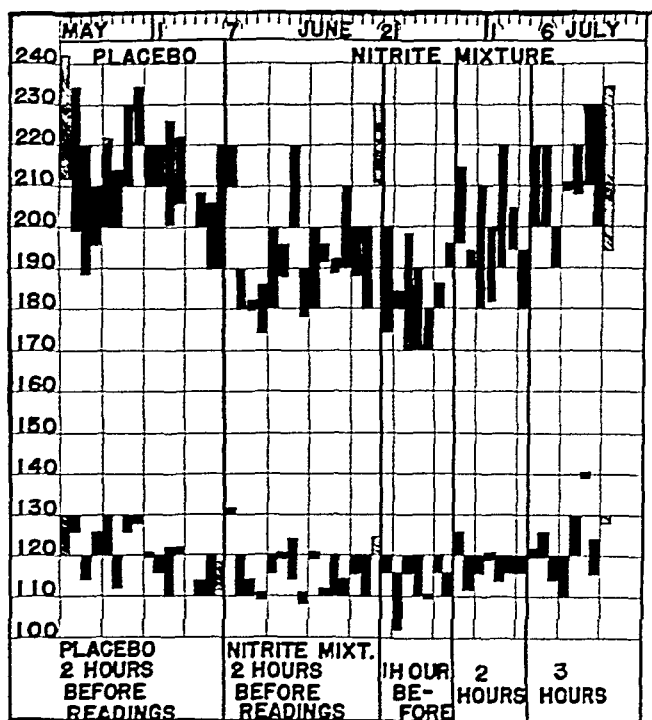
* Aided by a grant from the Charlton Fund. Tufts Medical School.

determination of the blood pressure at home was done accurately and without upsetting the patient. The accuracy of the home readings was checked as previously outlined.^{1a}

Drugs used included sedatives, nitrites, potassium thiocyanate, estrogens, and placebos. The effects of sympathectomy were also studied.

Results. We are reporting the common effect of different therapy rather than the effect of any particular drug or method.

1. *Evaluation of Slight Effects on the Blood Pressure Level.* Home blood pressure studies are of value in studying the effect of a form



blood pressure at home, whereas the clinic readings show no change. Since nitrites are obviously not continuous in action, their effect on the blood pressure could not be determined by clinic visits unless the drug were taken just prior to the clinic visit. In this instance, the blood pressure readings were taken at home at various intervals after taking the drug and it is possible, therefore, to note the fact that this drug had its greatest effect one hour after it was taken.

2. *Study of Small Number of Cases.* Study of home blood pressure readings has also permitted the satisfactory evaluation of drugs through the use of a small number of cases. It is apparent that results in a dozen cases studied by this method give more conclusive information than those in a much larger series studied by means of occasional clinic readings.

3. *Gives Better Understanding of the Toxic Reactions of Drugs.* Another important point clarified by the use of this method is the matter of untoward or toxic reactions to drugs. We have noted frequently that in one patient a very moderate amount of drug may give toxic reactions without any apparent drop in the clinic blood pressure, whereas in another patient the same dose and the appearance of toxic symptoms are accompanied by a drop in clinic blood pressure. It appears, therefore, that possibly in both cases the home blood pressure has dropped with the appearance of toxic symptoms, but has not been shown by the clinic readings in one case.

4. *Removes the Pressor Effect of the Physician's Presence.* The satisfactory effect of treatment is frequently masked by considering only the clinic blood pressure readings. This finding has been observed with all forms of therapy that have any effect. Figure 2 shows the blood pressure before and after sympathetic resection. Prior to operation the blood pressure in this patient was high both at home and in the clinic, although even before operation the clinic readings were higher than the home readings. Immediately following operation the home blood pressure readings dropped to normal while the clinic readings continued to be elevated and for the 2 years up to the time of writing (Nov., 1940) have continued so. It is evident, therefore, that consideration of only clinic readings in this case would have led to the conclusion that the patient still was constantly hypertensive, although there also had been a drop from the previous clinic level of around 250 to the present clinic level of 180 or so. In reality, however, this patient now has a normal blood pressure in the normal environment of her home. Similarly, in Figure 3, representing the effects of the administration of sulphocyanate, the blood pressure at home fell within a few days after beginning the use of this drug, but when the patient returned to the clinic no effect was noted in the clinic blood pressure (v., mark x in Fig. 3). On the next visit to the clinic there was some drop in the clinic blood pressure and further drop in the home readings. Without the home readings, therefore, one would have concluded that the blood pressure in this case had possibly dropped a little

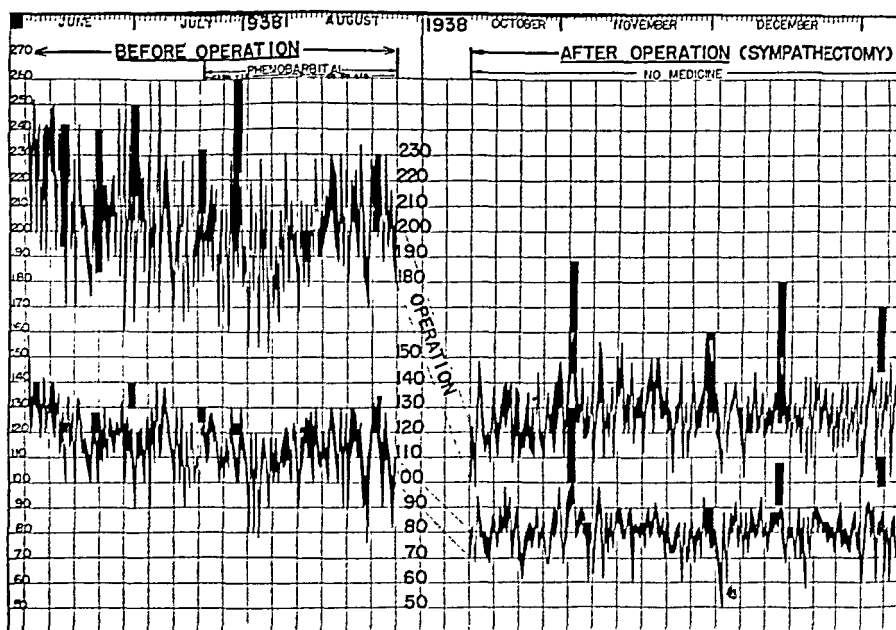


FIG. 2.—Home and clinic blood pressure readings, both before and after sympathectomy in a patient with essential hypertension. The black wavy curves are the daily home readings: the upper black curve the systolic and the lower black curve the diastolic. The vertical broad black bands are the clinic readings.

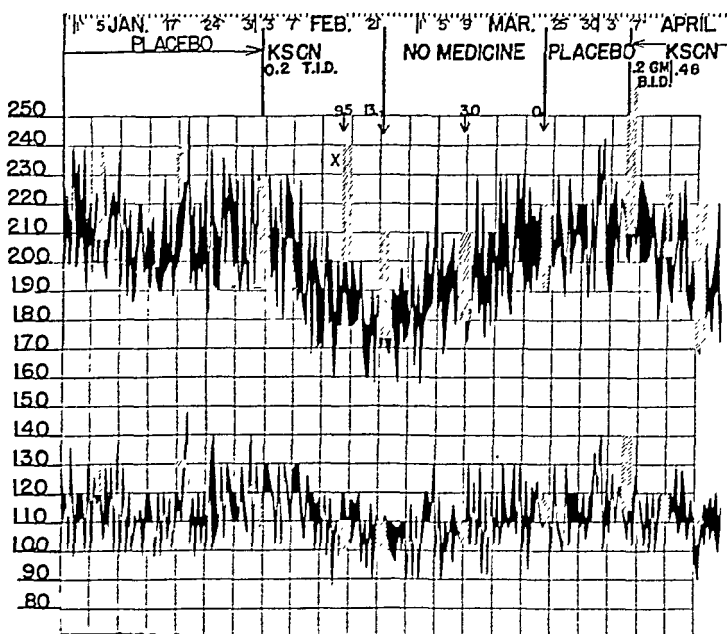


FIG. 3.—Home and clinic blood pressure curves of a patient with essential hypertension before, during and after treatment with potassium sulphocyanate. Explanation as in Figure 2. The numbers just above each arrow are the blood concentration of the potassium sulphocyanate in mg. per 100 cc. Each cross-hatched column represents clinic readings.

with the drug. However, from study of the home readings in this particular example it is clear (1) there is drop in blood pressure as a result of treatment; and (2) there is a steady rise in blood pressure following the cessation of the drug. Similar conclusions can be made from Figure 1 representing the effects of nitrites.

The difference between home and clinic blood pressure readings is due, we believe, to the fact that the doctor is a form of standard pressor stimulus similar to breath-holding^{1b} or cold.² The operation of this stimulus overcomes the hypotensive effect of drugs or operation. On removal of this stimulus and the determination of the blood pressure at home by a member of the household or the patient himself, the hypotensive effect of therapy becomes evident. In several instances where much lower readings at home were reported, we visited the patients at home and watched while the readings were taken. In the doctor's presence these home readings were as high as those found in the clinic. Also, in all patients after we had finished taking the clinic readings, we checked their blood pressure with a double stethoscope while they themselves took the readings in the clinic, and these readings usually were the highest readings found. It may be argued that this pressor effect of the physician's presence should not be considered active in cases who have been seen month after month for years, because such patients have become accustomed to the physician. It is our experience that a patient with essential hypertension can no more become non-reactive to the physician by repeated visits than he can become non-reactive to the pressor test of cold or breath-holding. Figure 2 is an example of the failure of the development of immunity on the part of the patient to the physician's presence despite 30 visits to the doctor in 2 years.

Summary and Conclusions. The study of home blood pressure levels furnishes a valuable means for judging the effect of treatment, because of the larger number of blood pressure readings obtained at home and the absence of the pressor effect of the physician's presence. It is, apparently, not possible for the patient to develop an immunity to the pressor effect of the physician's presence on his blood pressure. The findings of this study indicate that many drugs that in the past have been regarded as without effect must be re-studied since some of them may have hypotensive effects on the home blood pressure and no discernible effect on the clinic readings. Since the patient is living the greater part of his life in an environment similar to his home, it is reasonable to accept that the home readings are a more important indication of the patient's blood pressure than the clinic readings.

We wish to thank the Baumanometer Company for the loan of mercury blood pressure machines.

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AZOTEMIA DUE TO INGESTION OF BLOOD PROTEINS.

BLOOD UREA INCREASE RELATED TO INGESTION OF WHOLE BLOOD, RED CELLS, PLASMA, AND OTHER PROTEINS.

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THE increase in blood urea nitrogen which occurs following hemorrhage into the upper gastro-intestinal tract has been the cause of much speculation among clinicians. Numerous observations on clinical cases have excluded shock, dehydration, and starvation as possible underlying factors and renal clearance studies in uncomplicated cases have failed to demonstrate any accompanying disturbance in kidney function.^{1,3,4,8}

The introduction of citrated blood into the stomach, jejunum and upper ileum in humans⁸ has indicated that the presence of blood in the upper gastro-intestinal tract is responsible for the observed rise in urea nitrogen. However, in such studies, all possible variable factors are controlled with difficulty.

Kaump and Parsons⁶ have recently published a series of experiments in which, using dogs, they were able to demonstrate a preliminary rise in urea nitrogen directly dependent on feeding whole blood and a secondary, slight, delayed rise wholly dependent on bleeding. These authors also present a comprehensive review of the recent literature pertaining to extrarenal azotemia.

The present study is concerned with the increase in blood urea nitrogen in normal dogs, receiving standard, adequate diets, following the additional feeding of whole blood, red blood cells, plasma, casein, and lean meat. The accumulated data indicate that an elevation of blood urea nitrogen occurs after feeding each of the above mentioned substances and that the increase is directly dependent on the amount of protein in the material fed, irrespective of its form. This indicates that the globin of the hemoglobin, which accounts for approximately 70% of the protein in whole blood, is readily digested.

Therefore, one may conclude that the elevation in blood urea nitrogen which follows gastro-intestinal hemorrhage is due primarily to absorption of the digestive products of the protein of the blood.

Methods. Normal mongrel dogs, vaccinated against distemper, were used. All the animals were well nourished and received standard diets adequate, in protein and caloric content, to maintain nitrogen equilibrium and body weight. The diets were given at a definite time except on the

days of additional feeding, when they were offered following collection of the 12-hour blood sample.

All fluid materials were fed by stomach tube and the solids fed were consumed within a period of a few minutes.

Blood to be fed was obtained from normal donor dogs using as anticoagulant 1 cc. of saturated sodium citrate for each 100 cc. Red cell suspensions and plasma were obtained by centrifugation of whole blood. The plasma was pipetted off and the cells were resuspended in saline. The volume was accurately measured in each instance and aliquot portions were taken for protein determination. This was done by the macro-Kjeldahl method. The protein content of lean ground round steak was taken as approximately 22.6%.² Purified casein containing 85% protein as determined previously in this laboratory was used.

Blood samples for urea nitrogen and non-protein nitrogen determinations were obtained by jugular puncture, 0.1 cc. of saturated sodium citrate being used as anticoagulant for each 10 cc. of blood.

One blood sample was taken immediately before the additional protein feeding and subsequent samples approximately 3, 7, 12 and 24 hours after the feeding. In certain instances when the urea nitrogen concentration was still considerably elevated after 24 hours, an additional sample was taken 6 hours later.

All urea nitrogen determinations were carried out by the aëration method of Van Slyke and Cullen.⁹ Non-protein nitrogen was determined by a modification of the micro-Kjeldahl method of Goebel, as described by Peters and Van Slyke,⁷ after precipitation of the protein with 5% trichloroacetic acid.

Experimental Observations. The clinical condition of all animals remained essentially normal throughout the experiments. In no instance was the appetite impaired and a slight gain in weight was usually noted. Intubation of the stomach was well tolerated. Vomiting occurred occasionally, however, following the feeding of plasma in excess of 400 to 500 cc. or large quantities of packed red blood cells and such experiments were immediately discontinued.

Tarry stools were usually noted during the 24 hours following the ingestion of whole blood or resuspended red cells. Slight diarrhea accompanied the tarry stools in a few instances.

Chart 1 shows the increases in blood urea nitrogen concentration following the ingestion of varying amounts of different materials, plotted against the hours of the experiment, in one representative series. It will be noted that the form of the curves is roughly similar in most experiments and that the time required to reach the peak is approximately proportional to the magnitude of the increase. This time interval varies from $4\frac{1}{2}$ to 10 hours. In every instance the urea nitrogen concentration returns to the basal level within 30 hours and in the majority of cases it is normal in 24 hours or less. Increases in non-protein nitrogen parallel those of urea nitrogen in every respect and may be accounted for almost entirely by the rises in urea nitrogen.

Table 1 lists the outstanding features of each experiment. Column 3 indicates the type and amount of material fed, while the protein content of each feeding is tabulated in Column 4. The maximum increases in urea nitrogen and non-protein nitrogen con-

centration listed in Columns 6 and 7 were derived from the type of curves illustrated in Chart 1. In the majority of cases the figure corresponds with an actual determination; however, others were obtained by interpolation when the experimental points were obviously not at the peak of the curve. Comparison of Columns 4 and 6 reveals that the maximum increase in urea nitrogen concentration (Column 6) varies in the same direction with increases or decreases in the total amount of additional protein ingested.

TABLE 1.—BLOOD UREA NITROGEN INCREASED BY FEEDING VARIOUS PROTEINS.

Dog No.	Weight, kilos.	Additional feeding, amount and type.	Protein content of feeding, gm.	Urea nitrogen concentration, mg. per 100 cc.		N.P.N. conc. max. increase above control, mg. per 100 cc.
				Control level.	Max. increase above control.	
38-189	13.8	300 cc. whole blood	63.0*	10.60	35.90	45.0
		137 cc. packed R.B.C.	40.0*	10.90	26.10	29.0
		160 cc. plasma	10.4*	10.80	7.62	
38-23	19.6	300 cc. whole blood	63.0*	7.11	17.00	20.4
		150 cc. whole blood	31.5*	5.77	7.00	7.4
		180 cc. whole blood	36.7	8.60	8.00	10.0
		310 cc. whole blood	72.0	9.12	13.88	16.3
		500 cc. whole blood	106.0	8.95	22.30	25.0
		126 cc. packed R.B.C.	33.3	12.70	7.50	10.5
		310 cc. packed R.B.C.	86.5	5.24	17.50	23.5
		395 cc. plasma	24.2	5.91	6.57	
		500 cc. plasma	34.6	6.65	6.20	10.4
		48 gm. casein	41.0	5.72	11.20	16.0
		260 gm. lean round steak	57.0	10.70	11.42	13.2
38-11	15.6	100 cc. whole blood	22.4	12.20	6.80	7.8
		175 cc. whole blood	36.6	11.62	14.00	22.5
		305 cc. whole blood	66.7	10.69	20.00	20.0
		60 cc. packed R.B.C.	24.4	11.50	10.65	10.9
		75 cc. packed R.B.C.	31.1	8.42	8.00	
		130 cc. packed R.B.C.	53.2	12.88	19.14	22.2
		275 cc. plasma	15.7	11.04	2.00	2.0
		440 cc. plasma	26.6	8.40	7.00	7.4
		440 cc. plasma	24.2	10.23	7.88	
		50 gm. casein	42.5	10.40	13.20	13.8
		200 gm. lean round steak	42.0	14.70	12.00	13.1

Figures in Column 4 marked * were estimated, not actually determined.

In Chart 2 the protein fed in each experiment is plotted against the corresponding maximum increase in urea nitrogen concentration. It is apparent that the maximum rise in urea nitrogen concentration bears a direct relationship to the protein content of the material ingested, irrespective of its form. In view of the generally similar shape of the curves representing increases in urea nitrogen concentration (Chart 1), the value for each maximum increase will be approximately proportional to the total increase in urea nitrogen occurring after each additional feeding. These values of course give no indication of the actual magnitude of the total increase in urea.

Discussion. It has been demonstrated by previous investigators that azotemia results directly from the presence of blood in the upper portions of the gastro-intestinal tract. In the present experiments all complicating factors are absent and the data show clearly that the effects of such blood on the urea nitrogen concentration can be duplicated by either the red cell or plasma elements of the

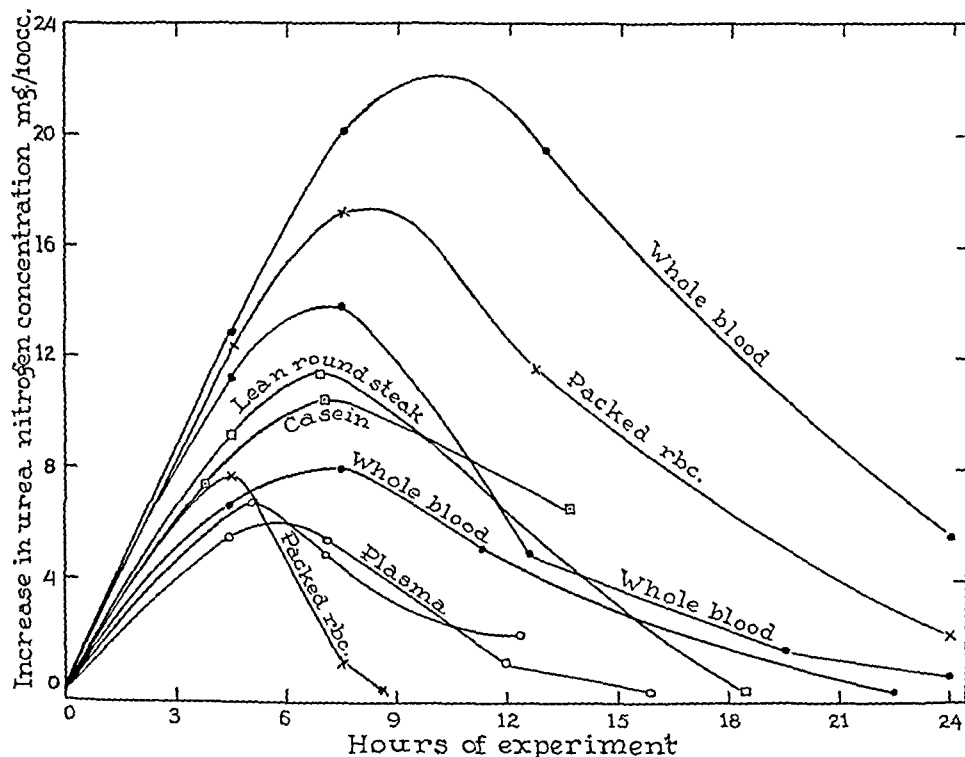


CHART 1.—Increases in urea nitrogen concentration above the control level, at varying time intervals after the ingestion of different materials.

blood, by a simple protein such as casein, or by lean meat rapidly consumed. In each case the maximum increase in urea nitrogen concentration is related directly to the protein content of the material ingested.

These findings also exclude the possibility of any toxic effect related to the absorption of breakdown products of blood as a cause of the rise in urea.

It has been assumed that hemoglobin is not digested to any great extent in the gastro-intestinal tract and this assumption has been supported by the occurrence of tarry stools following gastro-intestinal hemorrhage. It is clear from these experiments that globin, comprising 95% of hemoglobin, is as readily digested as any of the other proteins given. In certain experiments measurements were made of the excess nitrogen excreted by the kidneys during the periods of azotemia. The findings are not sufficiently complete to be included in detail, but it is interesting to note that

the most marked increases in urinary nitrogen were encountered during those experiments when the protein ingested was all in the form of *hemoglobin*. Since at times as much as 75% of the protein fed was accounted for by excess urinary nitrogen, *globin* is obviously

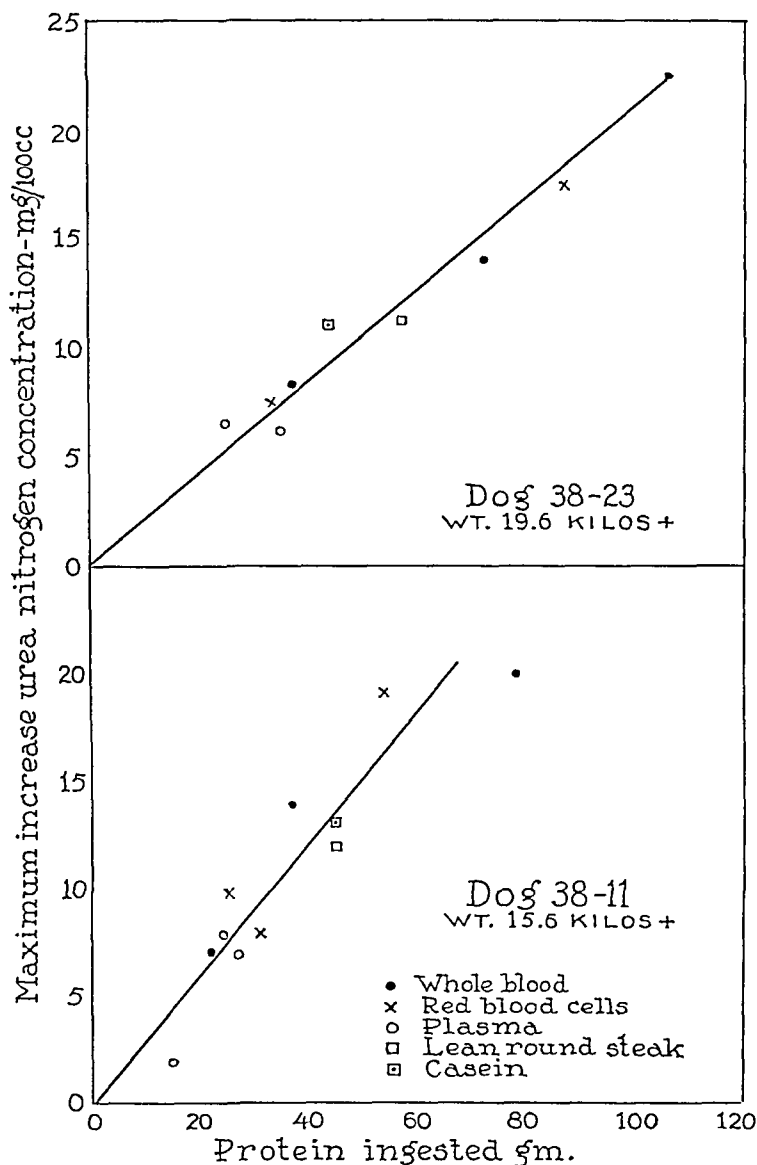


CHART 2.—The maximum increase in urea nitrogen concentration, above the control level, plotted against the protein content of the corresponding additional feeding, in two series of experiments.

digested and absorbed, though not utilized to any great extent. As a result of this, the tarry stools which follow gastro-intestinal hemorrhage probably contain largely the pigment portions of the blood. Non-utilization of the digestive products of hemoglobin have been observed previously in this laboratory. Hemoglobin

given by vein is utilized practically 100% to form new red cells by anemic dogs, as contrasted with a 10% recovery when similar amounts are fed.¹⁰

It has been suggested that the elevation of blood urea nitrogen may be used as a means of determining the continuance or recurrence of intestinal hemorrhage.⁵ The value of this procedure is doubtful since in massive hemorrhage other signs and symptoms are more obvious and important and the slight rises accompanying small hemorrhages may be readily overlooked. Food within the intestinal tract may also confuse the picture and nullify the significance of any elevation in blood urea nitrogen.

Conclusions. The concentration of urea nitrogen in the blood increases following the ingestion of whole blood and the magnitude of the increase is proportional to the quantity of blood given.

Comparable amounts of protein fed in the form of red cells, plasma, casein, or lean meat also cause similar increases in blood urea nitrogen.

It is apparent that the elevation of blood urea nitrogen is related to the digestion of these protein materials and absorption of the digestive products from the intestinal tract. The globin in hemoglobin is obviously digested as readily as any other protein.

Shock, dehydration, starvation, or impaired renal function are not necessary factors in the production of the azotemia observed following hemorrhage into the upper gastro-intestinal tract.

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THE ELECTROCARDIOGRAM DURING ELECTRIC SHOCK TREATMENT OF MENTAL DISORDERS.

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The convulsive treatment for schizophrenia and other psychoses, first insulin and later metrazol, has been used with favorable results

since its popularization a few years ago. Most recently, convulsions have been produced by means of electric shock. Due to its simplicity, favorable reaction of the patient and the good results obtained, this procedure has gained considerable popularity. Although there is considerable information in the literature concerning the effect of severe grades of electric shock upon the organism in general and upon the heart in particular, we have been able to find no reference concerning cardiac and particularly electrocardiographic studies in the less severe type of shock treatment. In view of the possible effects of this procedure on the heart, it was considered of interest to study the cardiovascular response and particularly the electrocardiographic alterations incident to this type of therapy.

Procedure and Apparatus for Inducing Electric Shock. In 1938, Cerletti and Bini,⁵ encouraged by preliminary experimental studies in dogs, announced their use of electrically induced convulsions for the treatment of schizophrenia. Several investigators^{2-4,6,7,13,16,17a,b} corroborated their findings and agreed that the method has definite advantages over other forms of convulsive therapy:

The apparatus devised by Cerletti and Bini⁵ and modified by Fleming, Galla and Walters,⁶ utilizes alternating current of 110 volts. Step-down and step-up transformers are so arranged that the voltage can be regulated from 0 to 220 volts. Metal salt-soaked electrodes are placed over the frontal poles of the head; utilizing a low tension circuit (4.5 volts), the voltage is adjusted so that approximately 1 milliamperes of current is delivered. The voltage is then read on a voltmeter and from Ohm's law ($\text{amperes} = \frac{\text{volts}}{\text{ohms}}$) the resistance is computed. This ranges between 450 and 1200 ohms. Exact calculation of the resistance is superfluous, as Cerletti emphasizes that Ohm's law does not apply to living tissues over a wide range of strong current strengths. The apparatus used in these experiments was therefore further modified so that the head resistance could be read directly on an ohmmeter with the voltage maintained at an empirical level (usually 80 volts). The high tension circuit is then turned on and an automatic timer which regulates the duration of flow of current from 0.1 to 1.0 is pressed. The average convulsive threshold ranges between 80 to 150 volts, 200 to 300 milliamperes and 0.25 to 0.50 second.

By this method of application, the electric shock passes through the animal body as though it were passing through a structureless gel, always choosing the shortest path from contact to contact without deflection by anatomic landmarks.¹⁸

The patient undergoing treatment may experience one of three reactions: 1. A momentary loss of consciousness preceded by a sudden start but without any muscular contractions. Sparks or

flashes of light may appear before the eyes, but the subject otherwise cannot recall what has happened to him. 2. A subconvulsive reaction. Following the start, facial twitchings appear and occasionally coarse tremors of the arms and legs. Unconsciousness lasts from 5 to 10 seconds. Mild cyanosis, sucking movements, confusion and verbigeration, singing or laughing may result. Amnesia for

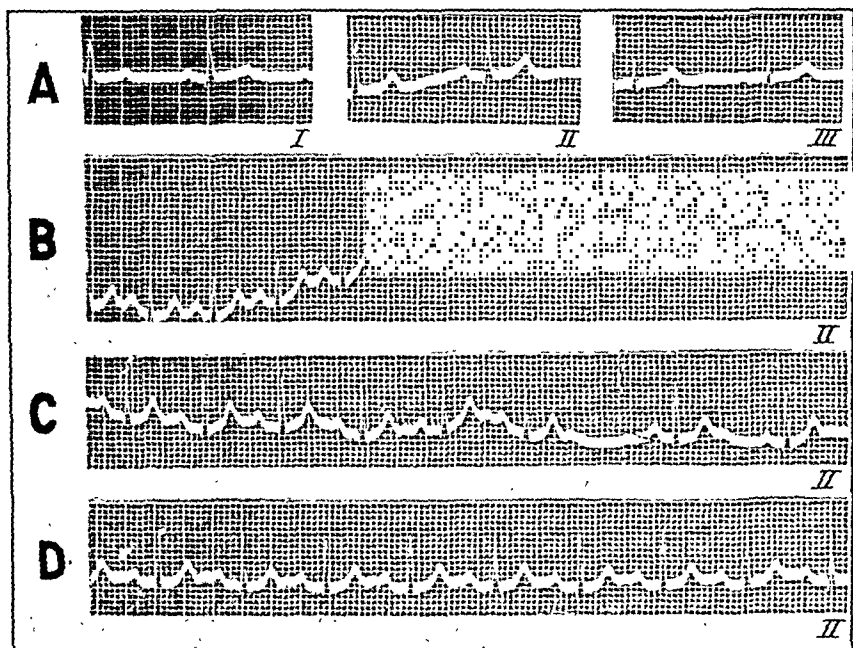


FIG. 1.—Represents typical changes observed. A, Leads I, II and III control, before electric shock. B, one minute after electric shock. The previous rate of 75 was increased to 145 per minute. C, Three and a half minutes after electric shock. Rate has slowed to 115 per minute. Occasional cycles of sinoauricular heart block. D, Four and a quarter minutes after electric shock. Normal rhythm, rate 107 per minute.

the episode is complete. 3. A convulsive reaction. There is a sudden severe generalized tonic spasm followed by facial twitchings, upward deviation of the eyes, pupillary dilatation, flexor tonus of the extremities, gradually giving way to clonic movements, apnea, cyanosis, salivation and finally hyperpnea. A cry usually does not occur. Amnesia is complete from the time of placing the electrodes to shortly after regaining consciousness.

Tonic spasm and a tendency to dislocation of the jaws is prevented by a suitable mouth gag and counter-pressure. Gentle restriction by holding the arms, hips and legs and maintenance of hyperextension of the vertebral column on a rigid wooden table may prevent fractures and dislocations.

The seizure lasts 30 to 45 seconds. A period of unconsciousness lasting 5 to 10 minutes follows the seizure and the patient passes through a short period of confusion before awakening. Restlessness,

nausea or vomiting after treatment are minimal in comparison with metrazol shock treatment. Sleep lasting 1 to 3 hours usually follows. Lassitude and moderately severe headache are frequent complaints, but these gradually give way to a feeling of well-being. Fear of treatment is rarely encountered.

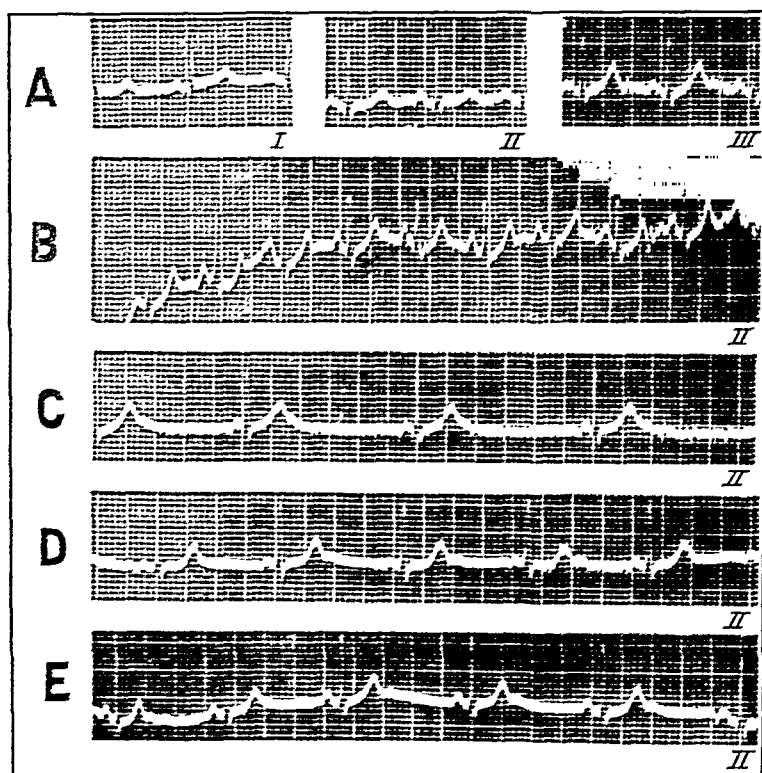


FIG. 2.—A, Leads I, II and III before convulsions. B, one minute after electric shock. Note increase in rate to 140 per minute. C, two and a half minutes after electric shock. Regular rhythm, rate 50 per minute. Short PR intervals, measuring 0.08 second, probably resulting from shift in pacemaker to lower portion of sinus node or to upper portion of A-V node. D, five minutes after electric shock: rate 72 per minute. P waves are still inverted but PR intervals now measure 0.12 second. The inverted P waves probably suggest that the pacemaker is situated in a different portion of the sinus node as compared to the normal. E, six minutes after electric shock; normal sinus rhythm, rate 68 per minute, P waves and PR intervals are now normal.

Choice of Patients. In our study, each patient was examined from the cardiovascular standpoint before therapy was instituted. This examination included orthodiagraphic and electrocardiographic studies. Only those patients in whom there was no clinical evidence of cardiac involvement were chosen. However, the presence of arteriosclerotic change in the older age groups could not be ruled out. Before application of the current, a control electrocardiogram (Leads I, II and III) was taken. During the convulsive seizure, where feasible, continual electrocardiographic tracings (Lead II)

were taken and at frequent intervals thereafter until the tracing returned to normal. This usually required 7 to 15 minutes from the onset of the convulsive seizure. In 3 cases in which electrocardiographic studies were made, 1/30 gr. atropine was administered subcutaneously before the shock. In 3 cases, curare was administered intravenously before the shock, 1 cc. per 15 pounds of body weight, for the purpose of diminishing the somatic effects of the convulsive seizure.

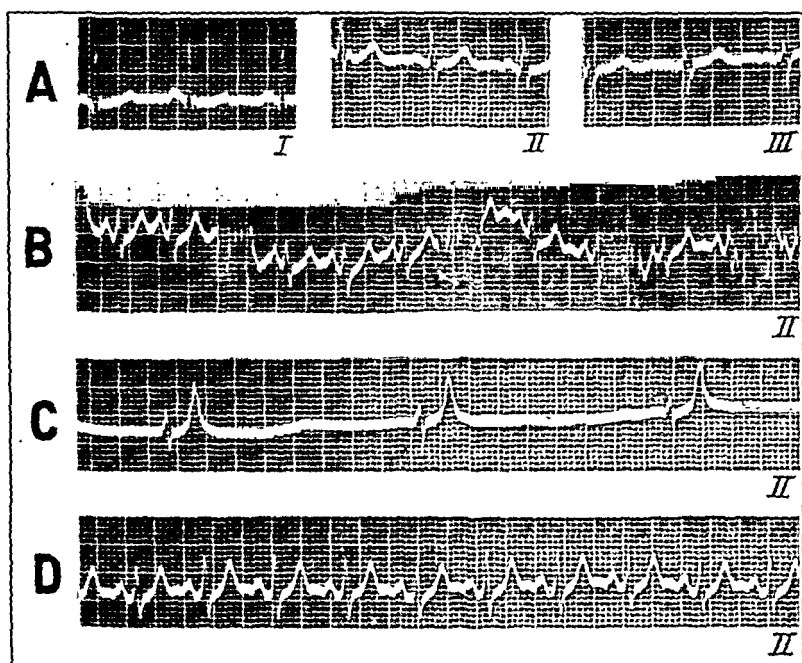


FIG. 3.—A, control, before electric shock. B, one minute after electric shock. Tachycardia, rate 150 per minute. C, two minutes after electric shock. Extremely slow ventricular rate, 35 per minute and absence of P waves. This is due either to long sinus pauses or an A-V nodal rhythm. D, five minutes after electric shock. Normal sinus rhythm, rate 125 per minute.

This report is based on 100 electrocardiographic studies during electric shock treatments in 50 patients, 65 of these studies were made on patients having major seizures and 35 on patients with minor seizures. The following were the age groups of our patients:

TABLE 1.—AGE GROUPS.

Age.	Cases.	Age.	Cases.
10-19	2	50-59	9
20-29	10	60-69	1
30-39	15		—
40-49	13	Total	50

Fourteen of our patients were male and 36 female. The mental disorders treated were: manic-depressive psychosis, 28; schizophrenia, 17; and psychoneurosis, 5.

Findings. Table 2 is a summary of the electrocardiographic changes which were obtained. In 12 studies, no electrocardiographic effects were detected. All 12 patients who showed no electrocardiographic effects had developed only minor seizures. Eighteen of the 22 patients who showed no increase in rate, had developed only minor seizures. In the group having major seizures, there was no definite correlation between the severity and length of the convulsive seizure and the grade of electrocardiographic effect. Likewise, there was no apparent relationship between the electrical dosage utilized in producing a convulsion and the severity of the electrocardiographic effects.

TABLE 2.—SUMMARY OF ELECTROCARDIOGRAPHIC EFFECTS.

	No. of observations.
<i>Minor disturbances in rhythm:</i>	
Sinus arrhythmia	26
Sinus bradycardia	7
Sino-auricular block	4
A-V nodal rhythm	2
Shifting pacemaker	3
Auricular extrasystoles	1
Total	43
<i>T wave and ST changes in Lead II:</i>	
T wave inverted	2
T wave flat	7
T wave increased height	6
ST segment depressed	3
Total	18
<i>Changes in rate:</i>	
Increased in rate to 120 to 150 per minute	66
Decrease in rate (occurring alone) to 55 to 60 per minute	18
Total	84

Atropine and Curare Studies. In 3 cases atropine sulphate, 1/30 gr., was administered subcutaneously 30 minutes before the electric shock, to patients who had previously developed rather marked electrocardiographic changes following their seizures. One patient who had previously developed a sinus bradycardia, sinus arrhythmia and slow nodal rhythm, following atropine, merely developed a minor reduction in cardiac rate from 150 per minute to 140 per minute. A similar type of change was recorded in the 2 other patients who received atropine. The effects in these patients during previous treatment had consisted of sinus arrhythmia and a very slow sinus rate.

Curare was administered to patients prior to convulsive therapy in order to minimize the systemic complications occurring during a convulsive seizure, particularly fractures of the vertebræ. Curare does this by partial paralysis of the nerve endings in the skeletal muscles. Following its administration, however, impairment of the activity of the accessory muscles of respiration may often occur and may at times be conducive to long periods of apnea. Three

patients received curare (1 cc. per 15 pounds of body weight administered intravenously at a very slow rate) before the administration of the electric shock. In 2 of the patients (ages 15 and 30) the electrocardiographic changes following the convulsive seizures were of the same order as those recorded when curare was not administered; namely, a tachycardia followed by a sinus arrhythmia. The third case, a patient of 54 years, developed a more severe reaction, which will be discussed below.

Untoward Effects. Untoward effects during electric shock therapy were observed under unusual circumstances in 2 patients of 54 and 47 years, respectively. These are discussed below:

Case Abstracts. CASE 1.—T.M., a colored male of 54, was admitted to the psychopathic ward with a diagnosis of involutional psychosis. His medical history, including the cardiovascular history, was negative. Physical examination revealed no abnormalities. Serology was negative, as were other laboratory findings. Blood pressure was 148/74. The control electrocardiogram, taken 2 days before the treatment, was within normal limits, showing only very slight flattening of T_1 and T_2 . The orthodiagram was normal. The electrocardiographic changes following curare and electric shock are illustrated in Figure 4. This shows the development of an idio-ventricular rhythm with widened ventricular complexes and ventricular extrasystoles; 15 minutes elapsed before the electrocardiogram returned to normal. These effects suggest a rather serious type of myocardial disturbance. Electric shock given to the same patient without curare at several later dates did not produce the severe effects seen when the curare had been given.

The convulsive seizure following shock is often followed by a short period of apnea. Curare by its depressing effect on the accessory muscles of respiration could still further prolong this apneic period with resulting impairment in function at a time when the heart work is already considerably increased. Such effects would be obviously more serious in older patients with arteriosclerotic change in the heart muscle.

CASE 2.—F.D., a white female of 47, was admitted July 22, 1940, to the psychopathic ward with a diagnosis of involutional melancholia with suicidal tendencies. She was severely undernourished and on admission weighed 87 pounds, a loss of 100 pounds having occurred in the previous year. No symptoms were referable to the cardiovascular system. Examination revealed no evidence of abnormalities in the chest or abdomen. Blood pressure was 140/100. Laboratory findings, including urine, blood count and Wassermann test, were negative. Blood chemistry was normal. The basal metabolic rate was +3. Roentgen ray of the skull was negative. On September 7, electric shock treatment was given, resulting in a minor seizure. About an hour later, this patient developed a series of severe major convulsive seizures during which she became cyanotic, and artificial respiration was required. The administration of ether anesthesia and intravenous sodium barbital was required for their abolition. An electrocardiogram taken after the series of seizures ceased, showed little change from the control. Subsequent tracings, however, showed considerable change as shown in Figure 5. These consisted of the development of inverted T waves in Leads I, II and CF_4 , which after 6 weeks had not returned to normal. At no time did this patient complain of precordial pain or manifest

any signs of marked cardiac derangement, except for a minor drop in blood pressure to 120/90 and leukocytosis of 14,000. There was no increase in temperature at any time.

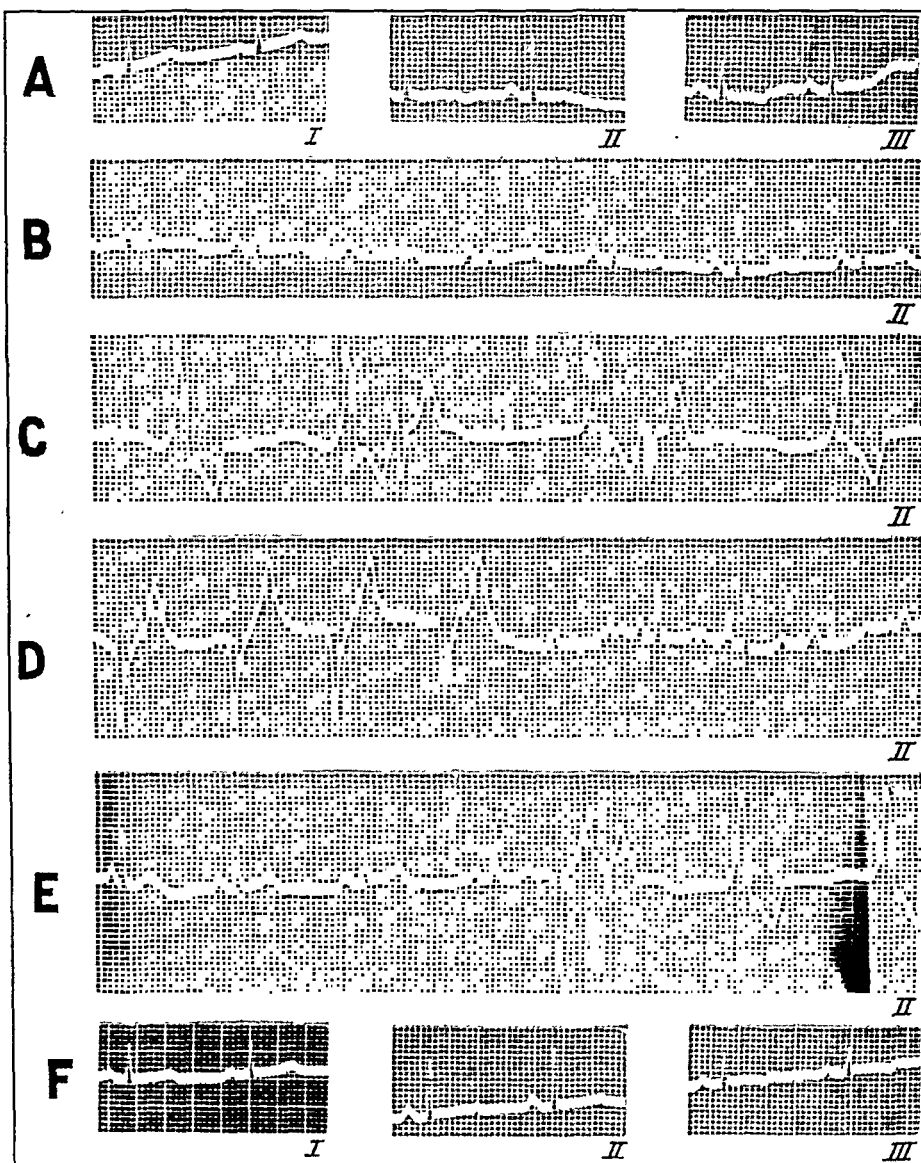


FIG. 4.—A, control, before electric shock. B, Lead II, 1 minute after curare 8.7 cc. was administered. Normal sinus rhythm is present with somewhat diminished amplitude of T waves. C, one minute after electric shock. Respirations shallow and slow. Idioventricular rhythm with aberrant widened ventricular complexes accompanied by frequent ventricular extrasystoles. D, four minutes after. Artificial respiration had been instituted. Aberrant ventricular complexes. Rate: 78 per minute, later merging into normal complexes with sinus rhythm. E, ten minutes after. Respirations still shallow and slow. Initial cycles of normal rhythm are followed by two ectopic ventricular beats occurring in succession, initiating a slow ectopic ventricular rhythm. Normal sinus rhythm has returned 15 minutes after electric shock had been given. F, normal rhythm, Leads I, II and III, as recorded 2 days later.

Delayed convulsive seizures such as were exhibited by this patient have been observed in occasional cases after metrazol and are probably related to the initial convulsion. The presence of the profound change in the electrocardiogram in this patient (Fig. 5) indicates that a severe derangement occurred in the myocardium. We are uncertain as to the condition responsible for these alterations. From postmortem examination of other cases dying in convulsive seizures, however, we know that it is possible that a hemorrhage into the ventricular musculature may have occurred. It is interesting that similar electrocardiographic changes have been reported by Levine, Piltz and Reznikoff¹⁴ following metrazol convulsions in 2 cases.

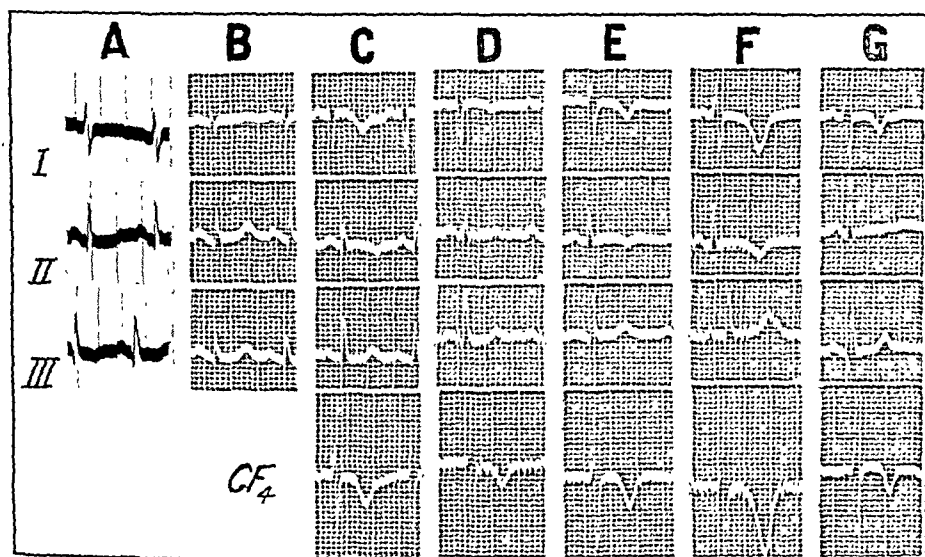


FIG. 5.—A, F.D., Case 2. September 5, 1940: Control. Note flattened *T* waves, depressed *ST* intervals in Leads II and III. B, September 7: one hour after series of convulsions. C, September 9: inversion of *T* waves in Leads I and II and *CF*₄ with tendency to right axis deviation. D, September 11: less marked inverted *T*₁, upright *T*₂ and *T*₃. E, September 17: resembles C. F, September 26: changes are more marked, inversion of *T*₁ and *T*₂ is rather deep, inversion of *T* and *CF*₄ is of considerable amplitude. G, October 24: *T*₁ still inverted, *T*₂ flat, *T*₃ upright, *T* of *CF*₄ still inverted.

Discussion. Certain electrocardiographic changes would not be unexpected in any type of convulsion. In that produced by electric shock, there are several factors that may influence the heart and the electrocardiogram: *a*, the strain upon the heart resulting from the mechanical effect of the convulsive seizure; *b*, certain reflex and indirect effects on the sympathetic and parasympathetic nervous systems.

As a result of the increased blood pressure which occurs during convulsive seizures, a great strain is suddenly placed upon the cardiovascular system. While in young individuals free from disease this usually is of little moment, the possible effect of such strain on the heart and vascular system must be taken into consider-

ation in older patients in whom arteriosclerotic changes are present. As a result of the sympathetic effect,* there is an increase in the cardiac rate, which usually ranges from 120 to 150 per minute. This increase is of short duration, lasting from 1 to 2 minutes. This increase in rate is usually followed by vagal effects with resultant slowing of the heart rate, which then drops to 40 to 60 per minute. Such effects are to be considered of a minor character and as the indirect result of vagal stimulation. They do not indicate any direct effect upon the muscle itself. Vagal effects were abolished in all 3 instances in which atropine was administered.

Comparison of the Effects of Insulin Shock, Metrazol and Electrical Shock on the Electrocardiogram. Convulsions occurring during insulin shock treatment are associated with a severe grade of hypoglycemia, dehydration and marked disturbance in the electrolytes. These changes occur at a time when the work of the heart is increased. As a result, severe strain upon the cardiovascular system is often induced and noteworthy electrocardiographic changes were obtained in two-thirds of a series of 58 shock treatments.¹ These were frequently of an order suggesting a severe type of myocardial derangement. The convulsions produced by the injection of metrazol are associated with cardiac strain but much less in degree than that due to insulin. The electrocardiographic changes are often slight, although more marked types of alterations are occasionally encountered, *e. g.*, *T* wave changes, auricular and ventricular extrasystoles and auricular fibrillation.^{10,15}

The alterations in the cardiovascular system produced by electric shock were much less severe than those in insulin convulsions and, except in the 2 instances cited, showed none of the more marked electrocardiographic changes observed with metrazol.

Although the number of studies performed in this series of experiments is not considerable, from the evidence so far accumulated it would appear that the convulsion produced by electric shock results in comparatively slight strain on the cardiovascular system.

Summary and Conclusions. The electrocardiographic alterations during 100 convulsive treatments produced by electric shock were recorded in 50 different patients. Of these, 65 were major and 35 were minor seizures. In this series, the electrocardiographic changes were of a minor degree in 98 shock treatments. These included minor arrhythmias, *e. g.*, sinus arrhythmia, sinus bradycardia, sino-auricular heart block in 35 instances, *A-V* nodal rhythm in 2, shifting pacemaker in 2, auricular extrasystoles in 1. Slight changes in the *T* and *ST* segment in Lead II were observed in 18 instances.

* Gellhorn,⁸ Gerard,⁹ Himwich,¹² Hartman¹¹ and others believe that the fundamental influence of convulsive shock therapy as well as hypoglycemic shock is through the production of cerebral anoxia. The deprivation of oxygen results in powerful sympathetic stimulation. The vagal effects are probably related to the period of apnea which often follows the convulsive seizure.

In only 2 instances were more serious results encountered under unusual circumstances in older patients, ages 47 and 54 respectively. The first consisted of the production of inverted *T* waves in Leads I and II following a delayed convulsive seizure and the second a serious type of arrhythmia following electric shock after curare.

We are very much indebted to Joseph Hughes, M.D., Chief of Laboratory Service of the Pennsylvania Hospital, who devised and constructed the apparatus used in this work.

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CHANGES IN THE ELECTROCARDIOGRAM AND IN THE CARDIAC RHYTHM DURING THE THERAPEUTIC USE OF POTASSIUM SALTS.

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THE rôle of the potassium ion in cardiac physiology has been extensively studied since Howell⁵ indicated the influence of various cations on the automatic contractions of heart muscle. Mathison⁸ in 1910 first observed ventricular fibrillation during the administration of potassium salts to animals. By means of electrocardiograms Nahum and Hoff⁹ concluded that ventricular fibrillation was to be attributed to production of widespread block in all parts of the heart. Winkler, Hoff and Smith²⁰ were of the opinion that there was some highly specific effect of potassium on the heart muscle itself, not shared by skeletal muscle generally.

Chamberlain, Scudder and Zwemer⁴ showed that increase in the potassium content of the blood of cats was associated with lowering or inversion of *T* waves, auriculoventricular and intraventricular

heart block, auricular standstill or auricular fibrillation, and ventricular tachycardia or tachysystole, ventricular fibrillation and ventricular standstill. In patients with Addison's disease, Thomson^{18a} found increased amplitude of *T* waves when the serum potassium was high followed in some cases by decrease in amplitude when the level fell as a consequence of treatment. Bamber¹ in 1935 described inversion of *T* waves in a patient with syphilitic heart disease who received potassium iodide. More recently, Thomson^{18b} has observed changes in *T* waves, occurrence of first-degree heart block and of auriculoventricular rhythm on the administration of potassium chloride and potassium citrate to patients. In view of the trend in the therapeutic use of potassium salts these studies are especially significant. Sampson and Anderson¹³ advocated large doses of potassium salts in the treatment of auricular and ventricular ectopic beats and tachycardias. Barker² observed the diuretic action of potassium chloride in the relief of anasarca and his observations were confirmed by Keith and Binger.⁶ More recently potassium salts have been employed in the treatment of neuromuscular disease,^{7,19} in allergic states,^{3,12} and their use in the therapy of hypertension has its advocates.¹⁰ Stewart, Smith and Milhorat¹⁷ reported lengthening of the *P-R* time, prolongation of the *QRS* time and increase in the *Q-T* interval as well as change in the form of the *R-T* segments and in the amplitude and form of the *T* waves in the electrocardiogram when the potassium content of the serum was low during the paralytic phase of familial periodic paralysis. These changes were attributed to a modification of one of the fundamental properties of heart muscle, namely conduction, by the low potassium concentration. Reversal in form of the electrocardiogram to its usual configuration occurred together with disappearance of paralysis on the administration of potassium chloride by mouth and restoration of the potassium level of the blood.

Since electrocardiographic observations have given evidence of change in the behavior of heart muscle with variation in the potassium levels, we analyzed the records of patients in the clinic in whom electrocardiographic alterations had been recorded during the administration of potassium salts. We have observed 5 patients in whom abnormal electrocardiographic changes were associated with the administration of potassium salts when given in the usual therapeutic amounts. These changes were characterized not only by changes in contour of the complexes of the electrocardiogram but also the occurrence of abnormalities of rhythm. To 1 patient potassium chloride was given as a diuretic; to 3, potassium iodide was given in treatment of cardiac syphilis; and finally, to the other patient potassium iodide was given as an expectorant. No attempt was made to examine the records of all patients receiving potassium salts nor were these drugs given in an attempt to reproduce the changes encountered in course of routine therapy of patients. Ade-

quate control records were available in each of these patients. Several patients were excluded from the study because of the lack of adequate control records, or of the giving of digitalis at a time when it confused the patterns. The current use of potassium salts in therapeutics, including the widespread administration of potassium iodide to patients with syphilis, especially of the cardiovascular system, makes these observations timely.

Case Abstracts. CASE 1.—F. S., Hist. No. 228926, a male, aged 65, was admitted to hospital complaining of pain in the left chest. He contracted syphilis 22 years earlier and received 5 intravenous and intramuscular injections at weekly intervals. In March, 1939, when he fractured several ribs, a Roentgen ray revealed aneurysm of the aorta and the Wassermann reaction of the blood was 4+.

On admission to hospital, the other significant findings were as follows: The blood pressure of the right arm was 130/80 mm. Hg and of the left 100/84 mm. Hg; there were no signs of aortic insufficiency nor of congestive heart failure; there was no evidence of neurologic involvement.

Course. An electrocardiogram was taken on admission. Tachycardia and low-grade fever resulted when the patient was given saturated solution of potassium iodide, 2 cc. (2 gm. KI), three times a day. A second electrocardiogram was taken at the end of 1 month because of persistent tachycardia despite rest in bed. On discharge, the patient was followed in the Out-Patient Department and was given bismuth and neoarsphenamine. He tolerated therapy well and remained free of symptoms. He also received potassium iodide but the dosage was not recorded accurately nor was there a record of the pulse rate. In the analysis of his data, it appeared that tachycardia was associated with the use of potassium iodide and it was decided to test this opinion by repetition of the observations. Consequently, the use of potassium iodide was discontinued and at the end of 3 weeks an electrocardiogram was taken to serve as a control for subsequent as well as against earlier potassium effects. After he had been given 2 cc. of saturated solution of potassium iodide three times a day for 1 week, another electrocardiogram was taken. During this time, a skin rash appeared.

Electrocardiograms. On admission the electrocardiogram showed left axis deviation as the only abnormality (Fig. 1, *a*). After the patient was given potassium iodide for 1 month, the rate increased to 111 per minute (Fig. 1, *b*). The *T* waves decreased in amplitude and the left axis deviation disappeared. In the first record of a second series (Fig. 1, *c*), when potassium iodide had been withheld for 3 weeks, the heart rate decreased to 83 per minute, and the *T* waves increased to their former amplitude (Fig. 1, *a*). After the patient was given potassium iodide again for 1 week, the heart rate increased to 107 per minute. In this record (Fig. 1, *d*), the *T* waves were also of slightly lower amplitude. After the patient had not received the drug for 1 week, slowing of the heart rate to 91 per minute occurred (Fig. 1, *e*).

This patient with syphilitic aneurysm of the aorta was given two courses of potassium iodide. On each occasion increase in heart rate, decrease in the amplitude of the *T* waves and iododerma occurred only to disappear when the drug was discontinued (Table 1).

CASE 2.—J. L., Hist. No. 131140, a male, aged 64, was admitted to hospital on February 8, 1940, because of progressive shortness of breath for 1 year. The patient had been given 20 injections of salvarsan following an attack of gonorrhea at 39 years but denied any knowledge of syphilis or of positive serology. One year before admission he experienced exertional

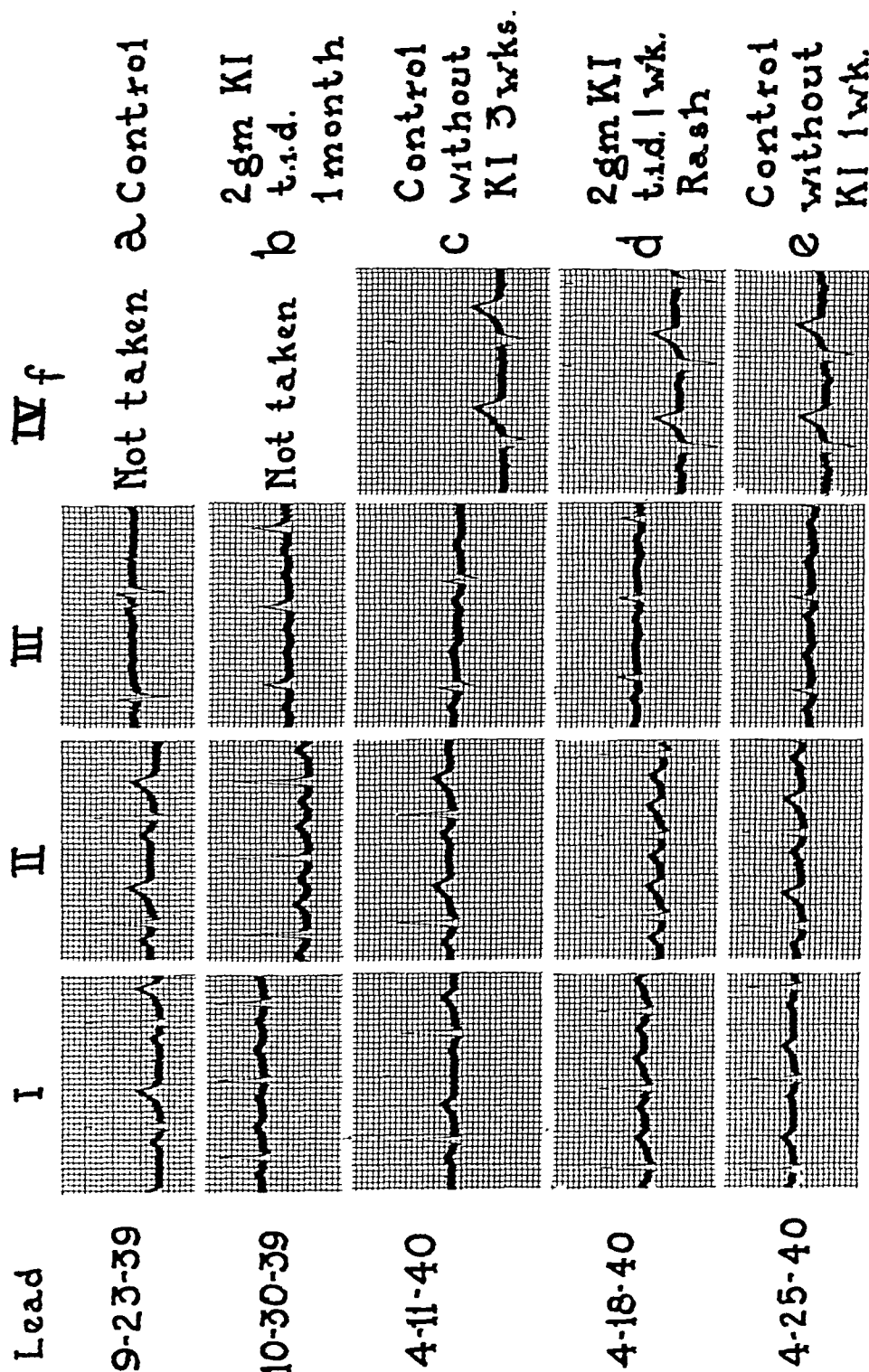


FIG. 1.—In this as well as in Figures 2, 4, 5, 6 and 7 are reproduced electrocardiograms derived from the three standard leads and Chest Lead IV f. The chest lead is the derivation recommended by the American Heart Association's Committee on Standardization of the Chest Lead.¹⁵ The standardization in all leads was such that 1 millivolt produced 1 cm. deflection of the string. Divisions of the ordinates equal 10^{-4} volt. Divisions of the abscissa equal 0.04 second. In this and the following figures KI = potassium iodide, KCl = potassium chloride, BaCl₂ = barium chloride, and CaCl₂ = calcium chloride. In this figure the electrocardiograms of F. S. (Case 1, Hist. No. 228926) are reproduced. For description see text.

TABLE 1.—COMPARISON OF RESULT OF GIVING POTASSIUM SALTS TO CATS AND TO PATIENTS IN THERAPEUTIC AMOUNTS.

	Heart rate.	T waves.	R-T segments.	A-V conduction.	Rhythm.		QRS conduction.	Result.
					Auricles.	Ventricles.		
Cats	Tachysystole	Lowering or inversion	Changed in form	Block	ANIMALS (4). Auricular fibrillation Auricular standstill	Vent. tachycardia Vent. tachysystole Vent. fibrillation Vent. standstill	Intraventricular heart block	Cessation of heart beat and death
Case 1 F. S.	Tachycardia	Decrease in amplitude	IN THIS SERIES ..	OF PATIENTS.*	Rash present. Changes disappeared with cessation of KI
	Tachycardia	Decrease in amplitude	Rash present. Changes disappeared with cessation of KI
Case 2 J. L.	Tachycardia	Decrease in amplitude	R-T ₁ changed in form	Rash present
	Tachycardia	Decrease in amplitude	R-T ₁ changed in form	Form of electrocardiogram reverted to normal with cessation of KI
Case 3 A. M.	Tachycardia	Decrease in amplitude	R-T _{1,2,3} depressed R-T ₃ elevated	Electrocardiogram resumed form before KI
	Tachycardia	T ₁ incr. ampl. T ₃ more neg.	R-T ₃ more diphasic R-T ₃ more depressed	Prolonged P-R time	Form of electrocardiogram reverted to normal when KI was discontinued.
Case 4 J. G.	Tachycardia	T _{1,2} more negative	R-T _{1,2,3} changed form	Prolonged P-R time	Complete A-V dissociation on 3 occasions	Irregular response of the ventricles; ? vent. fibrillation	..	Free of symptoms and abnormal rhythm after KI was discontinued
	Tachycardia	Paroxysmal supraventricular tachycardia	
Case 5 H. K.	Auricular standstill	Prolonged QRS time	Death

* The patients are arranged in the order of the severity of the toxic signs.

dyspnea, and ankle edema appeared at the end of the day. For 8 days preceding admission he suffered a respiratory infection. He was obese and had signs of pulmonary emphysema with superimposed bronchitis. The heart was enlarged to the left; there was no evidence of aortic or mitral valvular lesions. The blood pressure was 184/116 mm. Hg. The peripheral vessels were sclerotic. The signs of cardiac failure were slight edema over the sacrum and ankles, and enlargement of the liver. There were no signs of syphilis of the central nervous system.

Course.—The patient was kept at rest in bed with limited fluid and low salt intake and became free of signs of failure without the use of digitalis or other diuretics. Two cubic centimeters of saturated solution of potassium iodide (2 gm. KI) was administered three times a day as an expectorant. During hospitalization signs of congestive failure and coronary pain did not occur. The patient left the hospital against advice.

Electrocardiograms. An electrocardiogram taken shortly after admission revealed left axis deviation with normal sinus rhythm as well as normal conduction times (Fig. 2, *a*). There was low amplitude of the *T* waves in all leads including the Chest Lead IVf. The patient had received 4 gm. of potassium iodide 12 hours before this record was taken. After he had received 2 gm. of potassium iodide three times a day for 4 days, the heart rate increased (Fig. 3) and he exhibited an iodide rash. In an electrocardiogram taken at this time (Fig. 2, *b*), the heart rate was 107 per minute, *R-T*₁ had changed markedly in form and *T*₁ had become diphasic and *R-T*₄ had changed form and *T*₄ had become diphasic. At this time we were not fully aware of the effects of potassium salts given in therapeutic amounts on the form of the electrocardiogram and it was the opinion that he may have sustained recent coronary occlusion or pulmonary infarction. When the drug was discontinued for 4 days, however, *T*₁ increased in amplitude, changed form and became upright as did *T*₄ and the heart rate became slow, so that the electrocardiogram assumed a normal configuration except for the presence of left axis deviation (Fig. 2, *c*). There were now no deformities to suggest coronary artery disease. This record (Fig. 2, *c*) served as a control for this patient. The patient was then given the drug, potassium iodide, 6 gm. daily, for 2 days, and *T*₁ decreased in amplitude, *T*₃ changed form and the heart rate increased again (Fig. 2, *d*).

Second Admission. The patient was readmitted to the hospital on April 2, 1940, complaining of recurrence of dyspnea, edema of the ankles and sense of weight in the abdomen. There was a small amount of fluid in the peritoneal cavity.

Course. The regimen was similar to that instituted on the first admission. On this occasion, however, because of cardiac failure, 1.8 gm. of digitalis was given in 24 hours. During the administration of digitalis, electrocardiograms were taken. When the electrocardiogram had attained a stable form, potassium iodide was given again and records were taken daily. After receiving 2 gm. of potassium iodide three times a day, he suffered a low-grade fever and an iodide dermatitis.

Electrocardiograms. After the patient had received 1.8 gm. of digitalis, an electrocardiogram was taken. In this record (Fig. 4, *a*), as well as the electrocardiogram while he was maintained on 0.2 gm. of digitalis daily (Fig. 4, *a'*), the *T* waves were diphasic in Leads I, II and IV F, and the *R-T* segments depressed, changes characteristic of digitalis effect as described by Stewart and Watson.¹⁶ These two records were similar in form and served as controls. The heart rate was 100 per minute.

After receiving potassium iodide for 1 day only, *T*₁ and *T*₂ increased slightly in negativity. One left ventricular premature contraction was recorded in Lead III (Fig. 4, *b*). After 3 days on potassium iodide, marked changes were observed. The *T* waves increased in amplitude in all leads and

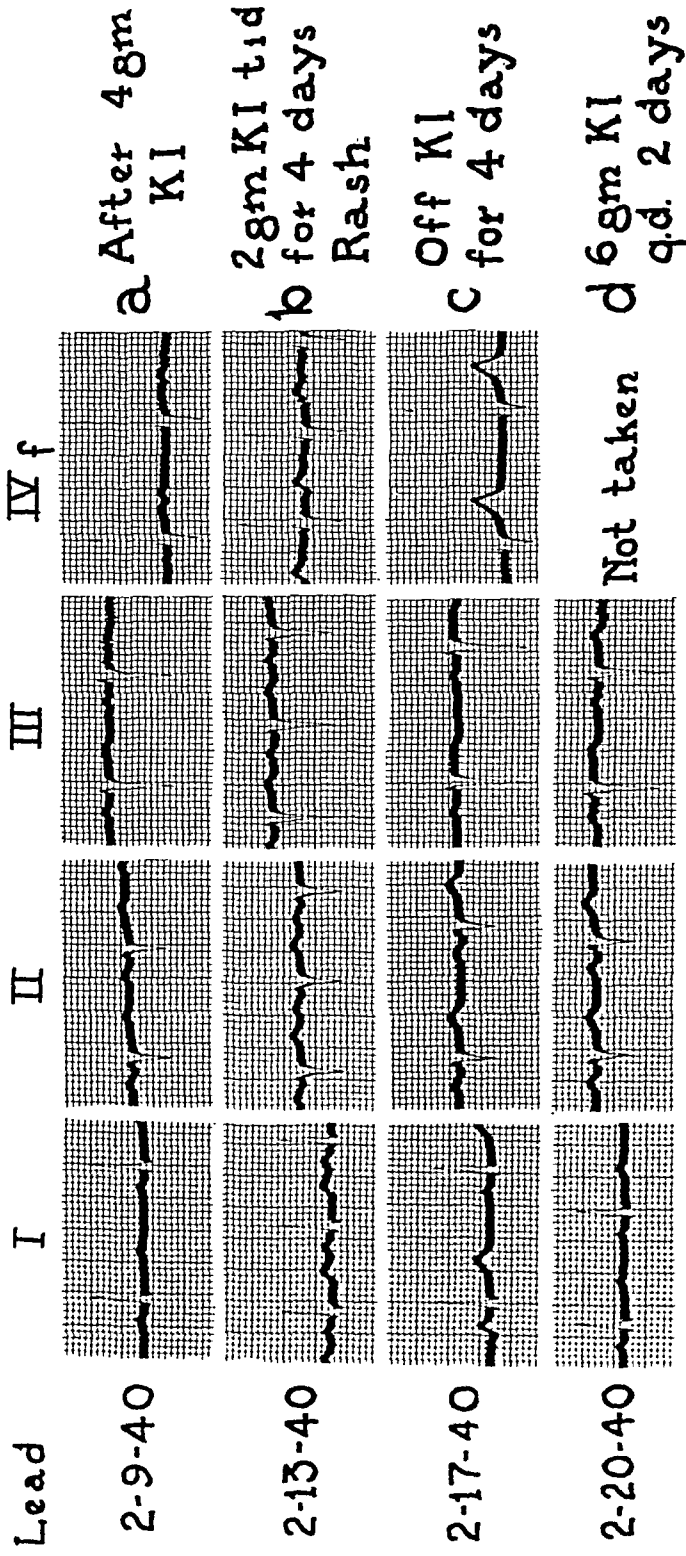


FIG. 2.—In this figure the electrocardiograms of J. L. (Case 2, Hist. No. 131140) are reproduced. For description see text.

$R-T_1$, $R-T_2$ and $R-T_4$ were much more depressed, $R-T_3$ now slightly elevated and a prominent Q_4 was present (Fig. 4, c). The heart rate increased to 125 per minute. When the drug was discontinued the electrocardiogram reverted to the form (Fig. 4, d) it exhibited before potassium iodide was given (Fig. 4, a¹).

In this patient suffering from hypertension, emphysema, chronic bronchitis and mild congestive heart failure, the administration of potassium iodide induced tachycardia and alterations in the form of the T waves and $R-T$ segments of the electrocardiogram which are usually thought to be associated with recent coronary occlusion. These changes were reproduced on a second occasion when potassium iodide was given. Iodide rash also occurred.

CASE 3.—A. M., Hist. No. 252085, a male, aged 48, was admitted to hospital on December 6, 1939, complaining of dull pain in the chest and back for 2 weeks. The patient had a chancre in 1920. Sometime later, because of a "positive blood test," he was given 5 "intravenous injections." Two years before admission he first experienced mild exertional dyspnea which increased until he could climb only two or three flights of stairs without discomfort. At rest in bed the patient was not dyspneic. The heart was enlarged; a short blowing diastolic murmur heard over the base and transmitted down the left sternal border was evidence of aortic insufficiency. There were no signs of congestive heart failure. There were no abnormal neurologic findings. Kline and Wassermann reactions of the blood and spinal fluid were negative.

Course. The patient was given 2 cc. of potassium iodide solution (2 gm. KI) three times daily from December 9, 1939, until his discharge on December 19, 1939. Electrocardiograms were taken before, as well as at frequent intervals during the administration of the drug.

Electrocardiograms. The first electrocardiogram showed left axis deviation, normal sinus mechanism, the heart rate 71 per minute (Fig. 5, a). The $P-R$ conduction time was slightly prolonged to 0.22 second while the QRS time was within normal limits. From the clinical records we were unable to ascertain whether the patient had taken potassium iodide before admission. In the second and thirds leads, the T waves were diphasic and the $R-T$ segments slightly depressed and slightly "coved." The chest lead was essentially normal in contour.

After the patient had received potassium iodide for 4 days, the form of the electrocardiogram underwent several changes (Fig. 5, b). The heart rate increased to 94 per minute. The $P-R$ conduction time increased to 0.26 second. In Lead I the T waves decreased in amplitude and T_2 and T_3 as well as $R-T_2$ and $R-T_3$ changed form. After the patient had been given the drug for 8 days, these changes progressed (Fig. 5, c). The rate was still 94 per minute, and the $P-R$ conduction time increased still further to 0.28 second. In Lead II the T waves increased in amplitude and were more clearly diphasic while T_3 was slightly more negative. Several months later an electrocardiogram was taken after the patient had not received potassium iodide for 1 month. This served as a control (Fig. 5, d). The $P-R$ conduction time was normal; the T waves in Leads I and II were no longer diphasic, but had increased in amplitude, and assumed normal configurations.

In this patient with syphilitic heart disease and aortic insufficiency, the electrocardiogram showed a slightly prolonged $P-R$ conduction time. After the administration of potassium iodide in therapeutic amounts, there resulted persistent and progressive first-degree heart block, increase in heart rate and changes in the form of the T waves and $R-T$ segments which at that time were interpreted as due to slow closure of a coronary vessel at the ostium. Several months later, after potassium iodide had been discon-

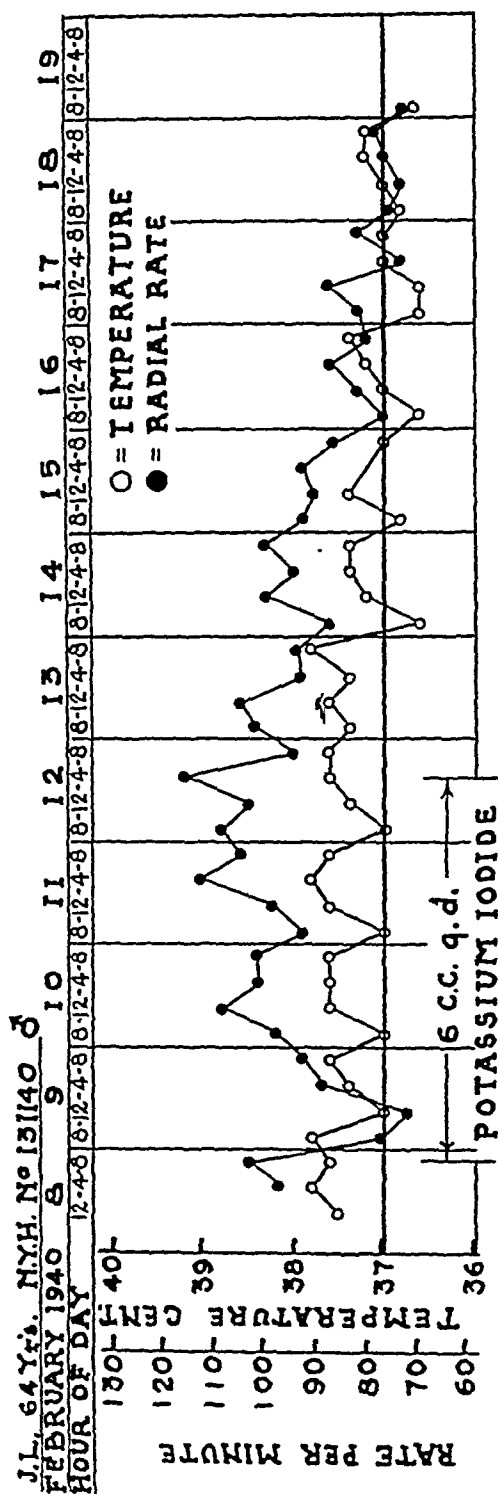


FIG. 3.—In this figure are reproduced the temperature and pulse records of J. L. (Case 2, Hist. No. 131140). The association between the administration of KI and tachycardia is apparent.

tinued, these changes were no longer present and the electrocardiogram was essentially normal in form.

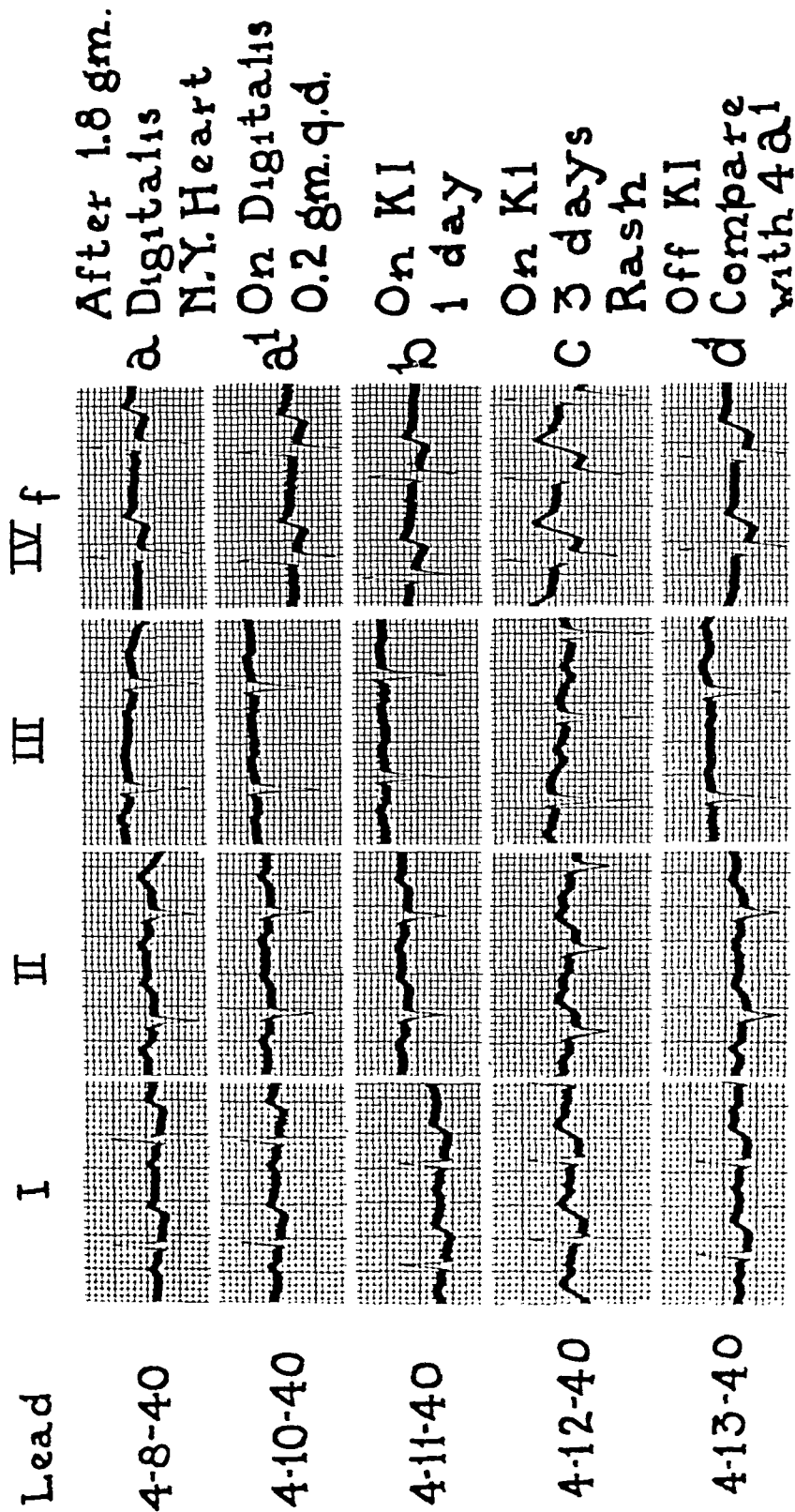
CASE 4.—J. G., Hist. No. 85687, a male, aged 46 years, was first admitted to hospital in February, 1935, complaining of shortness of breath on effort for 1 month. This symptom appeared for the first time on extreme exertion. He had experienced no palpitation, nor precordial distress. The patient denied having syphilis but admitted having contracted gonorrhea. The patient did not appear ill. The heart was enlarged to the left. The murmur of aortic insufficiency was heard, and Corrigan pulse, capillary pulse, Duroziez's sign and pistol shot sound were elicited. There were no signs of aortic aneurysm or of congestive heart failure. Blood and spinal fluid Kline and Wassermann reactions were 4+. When the diagnostic studies were completed, the patient was discharged and was followed in the Syphilis Clinic. His course over the 4 years between his first and his present admission was uneventful.

Under therapy, the spinal fluid Wassermann became negative. He remained free of cardiac symptoms. When he visited the clinic on April 28, 1939, the heart rhythm was described as "grossly irregular." On May 5, 1939, the patient was admitted to hospital because he was suspected of having suffered coronary occlusion, although he had experienced no symptoms indicative of this accident. He had occasionally suffered paroxysmal nocturnal dyspnea. There had been no significant change in physical signs of the heart. There was no rise in temperature, no elevation of leukocyte count, no acceleration of sedimentation time, no fall in blood pressure, nor other phenomena to indicate that he had suffered coronary occlusion.

Course. The patient was given potassium iodide, 2 cc. (2 gm. KI), three times a day beginning on May 8, 1939, the amount being reduced to 1 cc. three times a day on May 20, 1939. In addition, he received weekly injections of bismuth salicylate in oil. On May 23, 1939, after he had been given potassium iodide, 6 gm. a day for 12 days and 3 gm. a day for 3 days, he complained of rapid beating of the heart. An electrocardiogram was taken (Fig. 6, c) which showed transient complete auriculoventricular dissociation. On May 27, 1939, having received potassium iodide for 19 days, he complained of sudden palpitation. Although he experienced distress, it was not characteristic of coronary pain. The heart rate was rapid; the rhythm regular. An electrocardiogram revealed supraventricular paroxysmal tachycardia (Fig. 6, e). This attack terminated spontaneously within 5 hours but irregularity recurred 4 days later, May 31, 1939, and on this occasion was found again to be due to transient complete auriculoventricular dissociation (Fig. 6, f). Following this episode the administration of potassium iodide was discontinued. It was given again when he returned to the Out-Patient Clinic and once more disturbance in cardiac rhythm occurred. The use of the drug was then discontinued. Sixteen months later, October 7, 1940, the patient remained well, free of cardiac pain and of symptoms and signs of congestive heart failure. An electrocardiogram taken on April 22, 1940, was essentially similar to that recorded on May 1, 1939 (Fig. 6, a).

Electrocardiograms. On May 1, 1939, shortly after he had been observed to have a "grossly irregular" heart, normal sinus rhythm prevailed (Fig. 6, a). The QRS conduction time was increased to 0.11 second, just above the upper limits of normal. T_1 was diphasic, T_2 and T_3 were negative and "coved."

The record taken on May 15, 1939, after the patient had received potassium iodide for 8 days, showed normal sinus rhythm without change in the heart rate (Fig. 6, b). T_1 was still diphasic and had increased in negativity, the R-T segments had changed slightly in form in Leads I, II and III. The chest lead showed an abnormal configuration of R-T₄ and Q₄ was



(187)

FIG. 4.- In this figure the electrocardiograms of J. L. (Case 2, Hist. No. 1311-40), on his second admission, are reproduced. For description see text.

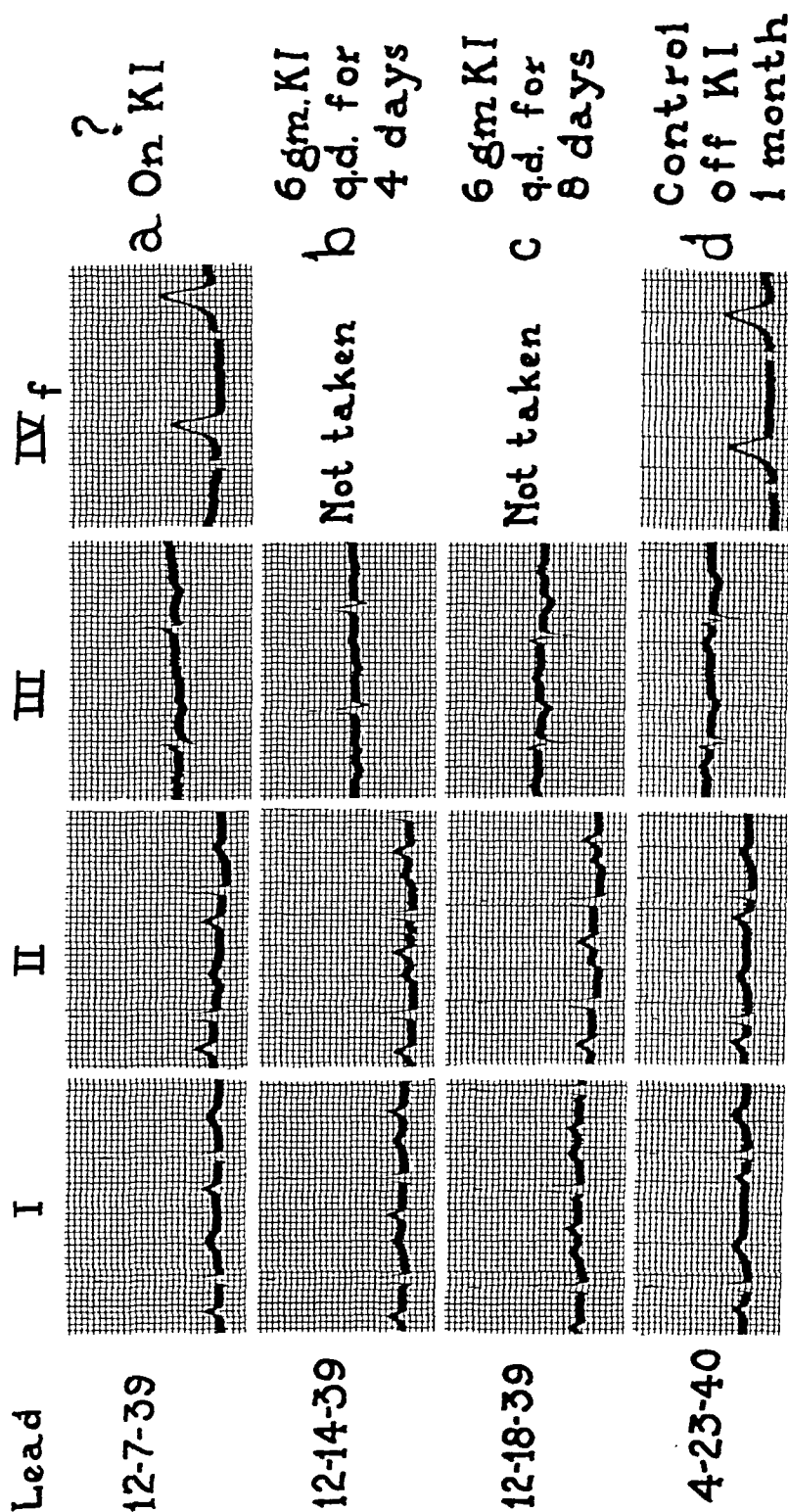


FIG. 5.—In this figure the electrocardiograms of A. M. (Case 3, Hist. No. 252085) are reproduced. For description see text.

present. In the electrocardiogram taken when the patient experienced palpitation, May 23, 1939, the heart rate was 115 per minute (Fig. 6, c). The form of Lead I was unchanged. In Lead II there were a few normal beats followed by a short run (6 complexes) of complete auriculoventricular dissociation with irregularity of the ventricular complexes, followed by recurrence of normal rhythm. In addition, the *T* waves in Leads II, III, and IVf had decreased in amplitude and the *R-T* segments changed in form. At that time, it was thought that these changes represented the evolution of the electrocardiogram following recent coronary occlusion.

Three days later, on May 26, 1939 (Fig. 6, d), the heart rate was 100 per minute, the rhythm regular. *T*₂ and *T*₃ were slightly more negative, *T*₄ changed slightly in form. When the patient experienced another attack of tachycardia the next day, May 27, supraventricular paroxysmal tachycardia was recorded (Fig. 6, e), probably nodal in origin, with the *P* waves buried in the *QRS* complexes. The heart rate was 130 per minute. The electrocardiogram on the following day was essentially of the same form as before tachycardia occurred (Fig. 6, d).

Four days later, May 31, 1939, the patient experienced still another attack in which the heart rhythm was irregular. In Leads I and II, there was complete auriculoventricular dissociation (Fig. 6, f) with irregularity of the ventricular complexes. In Lead III, block had disappeared and normal sequence restored for 3 beats, followed by recurrence of complete dissociation for 3 beats and then reversion to a normal sequence with prolonged *P-R* time. The administration of potassium iodide was discontinued and the patient suffered no recurrence of arrhythmia. The *T* waves and *R-T* segments now (Fig. 6, g) reverted to the form they presented at the beginning of the series (Fig. 6, a). While attending the Out-Patient Department, the patient received potassium iodide again sporadically. He suffered attacks of irregularity of the heart and on one occasion, December 29, 1939, there was recurrence of transient runs of complete auriculoventricular dissociation, with irregularity of the ventricular complexes, similar to that recorded in Figure 6, f. The patient was unwilling to take the drug longer and it was discontinued. Sixteen months after his last attack of paroxysmal tachycardia, he remained free of symptoms or signs of congestive heart failure without recurrence of irregularity.

This patient with syphilitic heart disease, luetic aortitis and aortic insufficiency, because of alterations in *T* waves and *R-T* segments and occurrence of disturbances of the cardiac rhythm, was thought, at first, to have suffered closure of a coronary ostium. Analysis of his data in relation to the use of potassium iodide, however, showed that these changes were associated with the administration of this drug. In him two abnormalities of rhythm resulted from administration of the drug: transient complete auriculoventricular dissociation, with rapid irregular sequence of the ventricles, and supraventricular paroxysmal tachycardia, probably auriculoventricular in origin.

CASE 5.—H. K., Hist. No. 6218, a female, aged 54, had three admissions to the New York Hospital. In 1924, a diabetic régime was instituted when glycosuria was found. Six years later, insulin therapy was begun. When first admitted in 1931, cardiac decompensation and renal insufficiency were discovered. She improved with use of digitalis and other diuretics; diabetes was regulated by diet and insulin and she was discharged 40 days after admission. In April, 1932, she was readmitted to hospital for 5 weeks because of advanced cardiac decompensation.

The patient's final admission, which was of interest in this investigation, was on September 23, 1932. She was dyspneic and had general anasarca. The heart was large; the sounds were distant and of poor quality. There was a rough systolic murmur over the precordium. The blood pressure

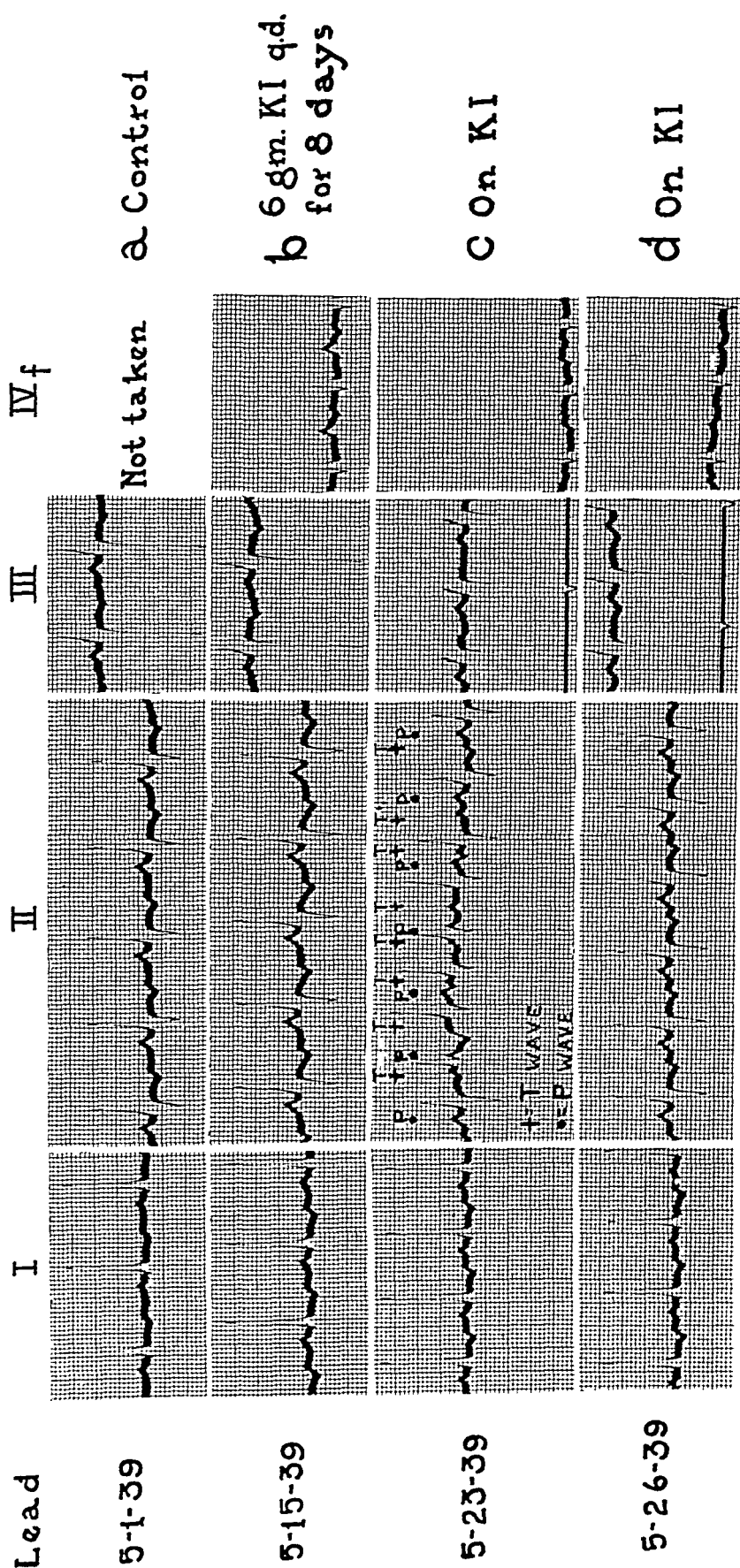
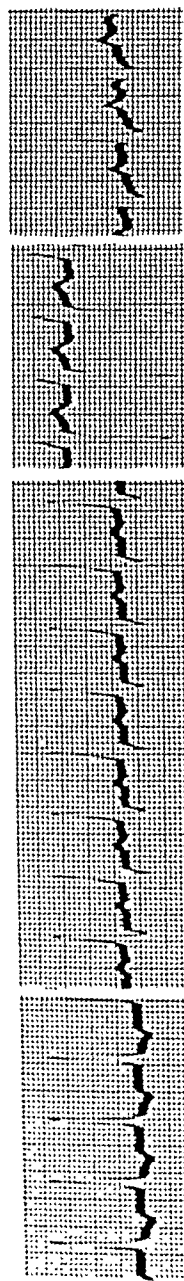


Fig. 6

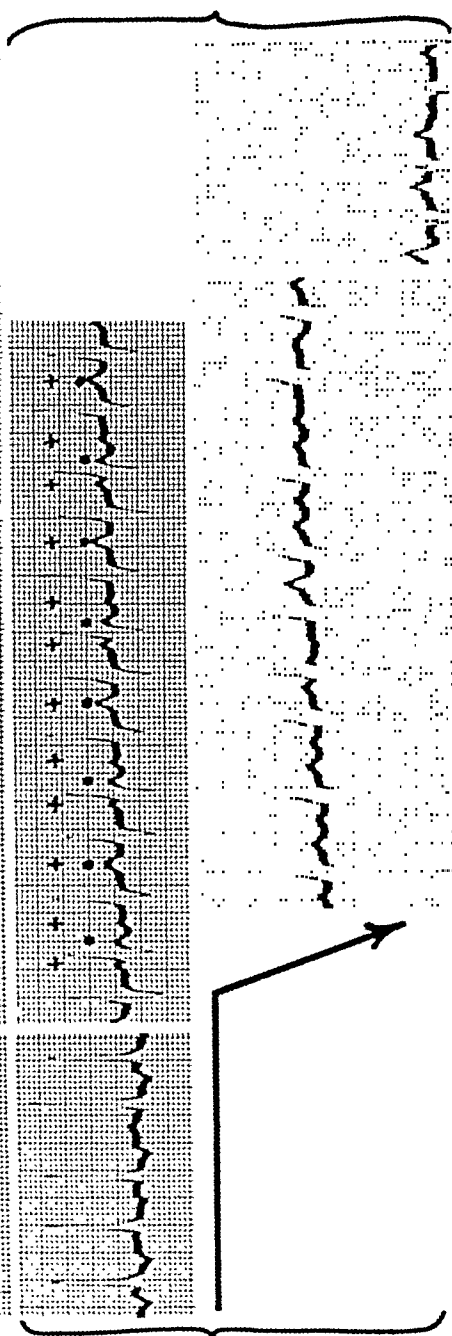
5-27-39

On KI



5-31-39

f On KI



6-12-39

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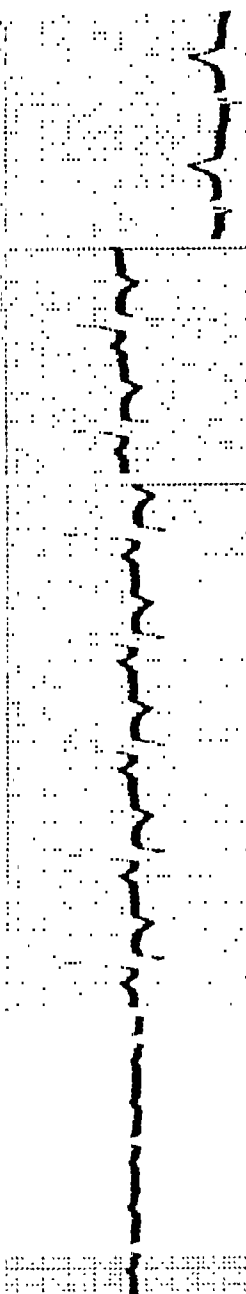


FIG. 6.—In this figure the electrocardiograms of J. G. (Case 5, Hist. No. 85687) are reproduced. For description see text.

was 210/115 mm. Hg. There was fluid in both pleural cavities. Ascites was present and the liver was felt 3.5 cm. below the costal margin. The specific gravity of the urine varied between 1.009 and 1.021 and albuminuria was a constant finding. Glycosuria was moderate and no ketone bodies were demonstrated in the urine. The urinary sediment contained a few white cells and a few hyaline and granular casts, but was free of red cells. There was microcytic anemia. The maximum blood sugar was 254 mg. per 100 cc.; acidosis was persistent with a carbon dioxide combining power which did not exceed 38 vol. % on any occasion. The blood urea nitrogen was 65 mg. per 100 cc., an elevation over the 40 mg. per 100 cc. previously recorded in April, 1932. The phenolsulphonephthalein excretion in 2 hours was 22%. The level of serum proteins was normal.

Course. During the first 3 weeks in the hospital the patient was given a total of 0.5 gm. digitan (Merck). On the twentieth hospital day, an electrocardiogram revealed auricular flutter. The heart reverted to normal sinus rhythm after 1.2 gm. digitan was given in 24 hours.

Although the patient was then given maintenance amounts of digitan, she became progressively worse. The use of insulin was continued; anemia did not respond to the use of iron. The administration of ammonium chloride, theocalcin, theocin, urea (50% solution) and salyrgan did not induce diuresis and edema increased. Two paracenteses abdominis yielded 900 cc. and 2000 cc. respectively. When the congestive failure persisted it was decided to test the diuretic action of potassium chloride. The patient received 5 gm. of potassium chloride daily for 3 days and 2.5 gm. on the fourth day. On the fifth day, 8 gm. were given. Several hours later the patient suddenly appeared to be ill, complained of weakness, fatigue and drowsiness. She was not dyspneic nor cyanotic; respirations were only slightly labored. The radial pulse rate was now found to be *36 per minute*. On auscultation the ventricular beats occurred regularly. Each systole was accompanied by three sounds which suggested the presence of intraventricular heart block with an asynchronism of the ventricles. The patient was given adrenalin intramuscularly without effect on the heart rate. The intravenous administration of calcium chloride increased the cardiac rate to 45 per minute for approximately one-half hour. The oral administration of barium chloride was without apparent effect on the irritability of the ventricular muscle and the patient died, approximately 7 hours after the onset of bradycardia. Electrocardiograms were taken at frequent intervals after the onset of bradycardia and during the use of the emergency measures which were employed.

Permission for autopsy was granted. The pathologic report was as follows: General arteriosclerosis, nephrosclerosis, cardiac hypertrophy and dilatation, chronic passive congestion of the lungs, liver, spleen and kidneys. There was general anasarca with ascites of 2500 cc., and each pleural cavity contained 750 cc. of fluid. The heart weighed 560 gm.; the coronary arteries were patent throughout, although in places the lumen was small. Microscopic section revealed small areas of localized hemorrhage in the muscle tissue. Microscopic section of the kidneys showed advanced thickening of the blood vessels, and less than one-third of the glomeruli appeared to be functioning. Many glomerular tufts showed fibrous replacement.

Electrocardiograms. Electrocardiograms, which are not reproduced, showed the change from auricular flutter to normal sinus rhythm after 1.2 gm. digitan had been given. Maintenance amounts of digitalis were continued. An electrocardiogram (Fig. 7, *a*), taken at this time, served as a control for our present analysis. Normal rhythm prevailed. The *P-R* and *QRS* conduction times were normal. *T₁* was negative, *R-T₁* slightly depressed and *R-T₂* slightly elevated. The form of the *R-T* segments probably indicated coronary artery changes, but from comparison with an

earlier record had been altered slightly by digitalis. On the fifth day after receiving potassium chloride, when the heart rate suddenly fell to 40 per minute, the *R-R* intervals in the electrocardiogram varied from 1.20 to 1.84 seconds (Fig. 7, *b*). Evidence of auricular activity could not be detected either in the three standard leads or in a chest derivation over the auricular projection on the chest. The ventricular complexes were grossly deformed, *QRS*, was greater than 0.24 second, and the duration of electrical systole was 0.70 second. It appeared that auricular standstill had occurred, a site in the left ventricle (old terminology) assuming the function of the pacemaker. That there was widespread interference with conduction was shown by the greatly prolonged *QRS* time, and the bizarre contour of these complexes. Adrenalin hydrochloride, 1 cc., intramuscularly produced no change in the form of the electrocardiogram or in the heart rate. Slight variation in the amplitude and form of the *QRS* complexes was probably due to differences in the pathway of excitation waves through the ventricular muscle.

Following the intravenous injection of 0.5 gm. of calcium chloride (Fig. 7, *c*), the heart rate rose to 45 per minute, the duration of electrical systole remained 0.7 second. A change in sequence of the *QRS* complexes occurred, so that they were now coupled, the shorter *R-R* intervals being 0.96 second and the longer ones 1.68 seconds. The ventricular complexes appeared to arise from the same site and the excitation wave to follow essentially the same course. The administration of barium chloride (0.03 gm.) by mouth effected no marked change. An electrocardiogram (Fig. 7, *d*) taken approximately 3 hours before death showed the same essential configuration, with the exception that the sequence of the *QRS* complexes was totally irregular.

In this patient who suffered from arteriosclerotic heart disease, nephrosclerosis and hypertension, the electrocardiogram taken after the administration of moderate doses of potassium chloride showed an absence of auricular activity. There was no deformity of the *QRS* complexes suggesting that *P* waves might be concealed in them nor was there any deformity when the *QRS* complexes occurred prematurely nor was there evidence of *P* waves or fibrillation waves in pre-auricular chest derivations. The use of adrenalin and barium induced no change. Calcium chloride increased the rate slightly and gave rise to coupled rhythm. The excitation waves appeared to arise in the left ventricle (old terminology). The form of the *QRS* complexes suggested that the excitation wave passed over devious pathways in being conducted through the ventricles.

Discussion. The experimental and clinical data which have been accumulated indicate the important part potassium plays in the physiology of heart muscle. We have observed effects in the electrocardiogram which were clearly to be attributed to this ion. Bizarre electrocardiographic changes during the paralytic phase of familial periodic paralysis appeared to be associated with low serum potassium concentration.¹⁷ We have now reported certain consequences of the therapeutic use of potassium salts in 5 patients. These patients exhibited tachycardia, paroxysmal tachycardia, bradycardia and iododerma as clinical manifestations of potassium toxicity. Moreover, certain electrocardiographic changes were observed. Sinus tachycardia was the simplest effect of potassium iodide on the heart, appearing in 4 cases. The heart rate returned to normal limits when administration of the drug was discontinued.

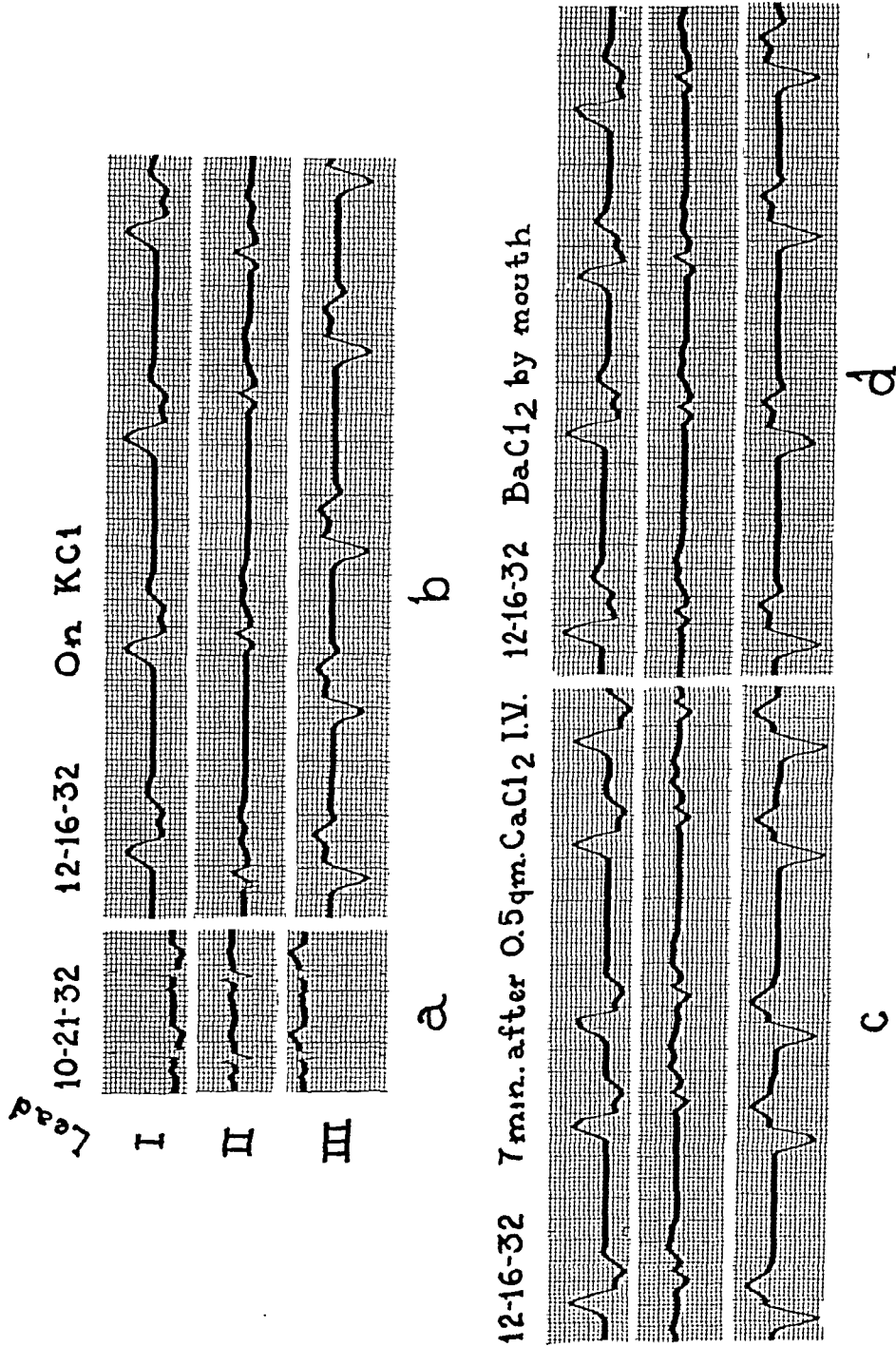


FIG. 7.—In this figure the electrocardiograms of H. K. (Case 6, Hist. No. 6218) are reproduced. For description see text. Pre-aortic chest derivations are not reproduced since they did not show evidence of auricular activity.

In 1 case (J. G., Case 4), the continued administration of potassium iodide induced complete auriculoventricular dissociation with irregularity of the ventricular complexes on 3 occasions. These electrocardiograms were somewhat similar to those which Nahum and Hoff⁹ and Chamberlain, Scudder and Zwemer⁴ published of ventricular fibrillation in cats resulting from potassium. On another occasion, supraventricular tachycardia, probably auriculoventricular (nodal) in origin, occurred in this patient. Thomson^{18b} also encountered this rhythm in his series. In A. M. (Case 3), persistent first-degree heart block occurred during the administration of potassium iodide. After the drug had been discontinued, the *P-R* conduction time fell to 0.16 second.

The changes in *T* wave now being reported differ from those recorded in patients suffering from Addison's disease in whom the concentrations of serum potassium is high. In them, the *T* waves are of increased amplitude and revert to normal with decrease in the level of serum potassium under cortin therapy. On the other hand, in the cases now being reported, the changes occur in the *R-T* segments and changes in amplitude may not be prominent. Our findings are in general agreement with those of Thomson.^{18b} Our patients were receiving the usual therapeutic dose of potassium salts, which is somewhat smaller than those given in the clinical observations which have been previously reported and proportionally smaller than those administered to animals. The presence of organic heart disease in these subjects may account for the ease with which toxic effects on the heart appeared.

Two of 3 patients suffering from luetic heart disease, A. M. (Case 3) and J. G. (Case 4), while taking potassium iodide showed changes in the form of the *T* waves and *R-T* segments which disappeared when the drug was discontinued. The changes in *T* waves in the electrocardiograms of these patients were attributed to coronary occlusion before their association with the use of potassium iodide was uncovered. When potassium iodide was discontinued the electrocardiograms reverted in form. In 1 patient (J. L., Case 2), moreover, the *T* waves were changed in amplitude and form when potassium iodide was administered alone as well as when it was given after the patient was digitalized. The early changes in the electrocardiogram of this patient were interpreted as due to coronary occlusion or possibly pulmonary infarction. Since patients with syphilitic heart disease frequently show changes in the electrocardiogram similar to those seen in coronary occlusion, it appears from the evidence now being presented, that some of these cases require reevaluation. The electrocardiographic effects may be induced by the administration of potassium iodide near the time of recording the electrocardiogram.

Rosenbaum and Levine¹¹ have called attention to the infrequent occurrence of auricular standstill. In our case, the onset of auricu-

lar standstill was precipitated by the use of potassium chloride as a diuretic. This case is of interest because the sequence of events in the cardiac rhythm duplicated that observed by Chamberlain, Scudder and Zwemer⁴ in animals. In 1915, Smillie¹⁴ described the impaired excretion of potassium in the presence of renal damage. In this patient, laboratory and postmortem data revealed advanced kidney disease. The marked renal lesion, no doubt, accounted for the appearance of such severe potassium effects on the heart in view of the relatively low dosage of potassium chloride.

The electrocardiographic changes which have been observed in these 5 patients receiving therapeutic doses of potassium salts are identical with those recorded by Chamberlain, Scudder and Zwemer⁴ when they increased the potassium level of the blood in cats (Table 1). Moreover, in the clinic we recorded 1 instance of supraventricular paroxysmal tachycardia which they did not encounter.

Summary. In 5 patients who received therapeutic amounts of potassium salts, we observed electrocardiographic abnormalities which parallel the changes seen in experimental animals receiving proportionally larger amounts of these substances. The following toxic manifestations were encountered: Sinus tachycardia, supraventricular paroxysmal tachycardia, complete auriculoventricular dissociation with irregularity of the ventricles suggesting ventricular fibrillation, progressive first-degree heart block and auricular standstill. These toxic effects with the exception of auricular standstill disappeared with discontinuance of potassium iodide. Three of the 5 patients showed changes in the form of the *T* waves and *R-T* segments which were ascribed to coronary occlusion until their association with potassium was detected. In 1 of these cases, the changes were reproduced a second time after full digitalization. In addition to digitalis (Stewart and Watson¹⁶), other drugs in common use, namely salts of potassium, are shown to induce electrocardiographic changes which may be confused with those usually attributed to coronary artery disease. Auricular standstill occurred in 1 patient who received potassium chloride as a diuretic. All of the changes we observed have also been observed in experimental animals when the potassium content of the blood was increased.

Because of the widespread use of potassium iodide in the treatment of cardiovascular syphilis and of hypertension, it is not out of place to emphasize that its use is not without danger as these changes in form of the electrocardiogram and in rhythm demonstrate. The most alarming toxic effect in its implications is the occurrence of a rhythm which has certain features similar to ventricular fibrillation. It is possible that certain accidents in patients suffering from syphilitic heart disease in the past may have occurred as a result of toxic effects of potassium on the heart.

Conclusions. From this study certain conclusions may be derived.

1. In addition to digitalis there are other drugs, namely salts of

potassium, which induce change in the *T* waves and *R-T* segments of the electrocardiogram that must be taken into account in the interpretation of electrocardiograms.

2. These changes in *T* waves and *R-T* segments may be confused with those usually attributed to myocardial damage resulting from coronary occlusion.

3. Rhythms of the heart having serious prognosis may result from the use of potassium salts in therapeutic amounts: (a) Complete auriculoventricular dissociation with irregularity of the ventricles simulating ventricular fibrillation and (b) auricular standstill.

4. The use of potassium salts may give rise not only to degrees of heart block ranging from prolongation of *P-R* interval to complete auriculoventricular dissociation, but also to intraventricular block and auricular standstill. These are evidence of toxic effects on the sinus node, and on the specific conducting systems of the heart.

5. These changes with the exception of auricular standstill, so far as can be ascertained from our experience, are reversible.

6. The use of potassium iodide in the treatment of syphilis should be carefully supervised if toxic effects on the heart are to be recognized and their occurrence prevented.

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CARDIAC DISEASE AMONG 28,139 NEWLY ENTERING STUDENTS AT THE UNIVERSITY OF WISCONSIN.

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THIS group of 28,139 individuals represents all of the new students who were admitted to the University of Wisconsin from July 1, 1931, to July 1, 1939, and each has had the benefit of a complete physical examination. In the event of suspicion or evidence of cardiac or other disease, thorough rechecking of the lesions was carried out.

The literature contains only a few reports on studies concerning cardiac disease in the college group, and Hedley⁷ comments that the literature is almost devoid of such material as the incidence of rheumatic heart disease among students in institutions of higher learning. His results are based upon answers to questionnaires sent to colleges and universities in this country (including the University of Wisconsin). Student health services have an exceptional opportunity to collect information and factual material of this nature, although relatively little of it finds its way into the literature.

The vast majority of heart disease in this age group is rheumatic in origin, but there are some few cases that are congenital and a very small number that are due to diseases of the thyroid and other causes.

As I have previously stated, each student is given a complete physical examination, and a careful history of present and past health is recorded. The individual is tuberculin-tested and vaccinated against smallpox (if his vaccination is over 5 years old). If the history is at all suspicious, if it includes rheumatic disease (and particularly rheumatic fever) or if there is a history of heart disease, we give that student an appointment for a recheck examination at an early date. In the meantime he is kept from participation in any sports or activities. The recheck examination is conducted in the quiet of our offices, where we have an opportunity to study the history and suspected lesion in more detail.

Where cardiac abnormality is discovered and the physician wishes consultation, electrocardiographic, orthodiascopic or other confirmatory study, we have the complete coöperation of the Department of Cardiology of the Wisconsin General Hospital.* These studies are made a permanent part of the individual's record and are a valuable addition for future reference and comparison.

Number of Students Examined With Figures Concerning Male and Female Hearts Diseased and Figures on Valvular Involvement. Table 1 represents a summary of students examined and the amount of heart disease found from July 1, 1931, to July 1, 1939.

TABLE 1.—FIGURES ON EXAMINATIONS PERFORMED AND HEART DISEASE DISCOVERED.

Total students examined July 1, 1931 to July 1, 1939	28,139
Total males examined (same period)	18,711
Total females examined (same period)	9,428
Total male hearts diseased	152
Total female hearts diseased	137
Total hearts diseased (male and female)	289
Incidence of heart disease per thousand students	10.2

When the figures in Table 1 are broken down on the basis of diseased hearts among males and among females in reference to their

* The Department of Cardiology is conducted by Dr. C. M. Kurtz, Dr. H. H. Shapiro and Dr. C. S. Mills, to whom acknowledgment is made for their valuable aid in the conduct of these investigations.

relative proportions, it is evident that the incidence among females shows a rather marked preponderance. These figures reveal 1.7 cases of female heart disease to 1 case of male heart disease. The preponderance of female hearts diseased has been a consistent finding in each of these 8 consecutive years.

Thompson and Niehaus¹⁷ have made the observation that while rheumatic heart disease shows a slight increase among female children, its incidence is about equal among adults of the two sexes. Hedley⁷ is of the opinion that sex is probably not a major factor in the distribution of rheumatic heart disease among college students. Jones⁸ states, in his discussion of the rheumatic child, that early signs of mitral stenosis are more frequent in the female child. It is possible that a larger number of cases collected over a longer period of time may show a somewhat different distribution of sex incidence of heart disease here at the University of Wisconsin.

The average age of the student entering the University with a diseased heart falls between 19 and 20 years.

TABLE 2.—RELATIVE FREQUENCY OF VALVES INVOLVED.

Valve.	No. of cases.	Percentage.
(1) Mitral valve involvement	263	91.0
(a) Regurgitation	217	75.0
(b) Stenosis	116	40.0
(2) Aortic valve involvement	45	15.5
(a) Regurgitation	40	13.8
(b) Stenosis	5	1.7
(3) Pulmonic valve involvement	2	0.7
(a) Regurgitation	0	0.0
(b) Stenosis	2	0.7
(4) Tricuspid valve involvement	0	0.0

Table 2 shows the incidence of valvular involvement and is in keeping with figures quoted by other investigators. These results agree with the observations of Wilson,¹⁸ Cleland,⁴ Christie³ and Cahan² concerning the relative frequencies of these particular valvular lesions, and it is thoroughly established that the mitral valve is involved in more than 85% of the cases and is followed next in order by the aortic valve. There is little clinical evidence in the great majority of cases of tricuspid and pulmonic valve involvement except in those cases where the tricuspid may show relative insufficiency (almost always a terminal or near-terminal event). However, autopsy reports reveal a considerably greater number of tricuspid valves involved in the rheumatic process and an occasional pulmonic valve, as noted by Wilson,¹⁸ Cleland,⁴ and Bland, White and Jones.¹

In a study of rheumatic heart disease among children, Seham, Shapiro and Hilbert¹⁵ have found in a group of 379 cases of organic heart disease that 74% were rheumatic, 18% congenital, 3.6% due to other causes, with 4.4% undiagnosed as to cause. They also state that in their group 92% of the cases of early mitral disease had historical evidence of rheumatic infection.

Congenital lesions were recorded as present in 8 cases in this group studied. Congenital cardiac disease predisposes to other heart involvement, and hypertension, subacute bacterial endocarditis and others are examples of these circulatory disabilities.

Table 3 shows the incidence of cardiac hypertrophy, hypertension and evidence of pericardial changes.

TABLE 3.—NUMBER OF CASES OF HYPERTROPHY, HYPERTENSION AND PERICARDIAL DAMAGE.

	No. of cases.	Percentage.
Cardiac hypertrophy	92	31.8
Hypertension*	46	15.9
Pericardial changes	17	5.8

* Cases were considered hypertensive if the systolic pressure was 150 mm. Hg or over, or the diastolic reading was 95 mm. Hg or over.

Cardiac hypertrophy was determined both by clinical means and by orthodiascopy. The orthodiascopic method has the considerable advantage of revealing the adequacy of the retrocardiac space which is of prognostic significance, we feel.

The orthodiagram has been a valuable record for our purposes because it reveals facts not clinically available, such as the frontal area, an accurate frontal diameter, the length of the left auricular salient and, in addition to the retrocardiac space, it gives evidence of certain congenital deformities and significant contour details.

Blood pressure readings have been given a somewhat greater latitude than are commonly allowed. The students are excited, due to the novelty of the experience of college matriculation; late hours are common because of the many social engagements during the first few days of college life; and nervousness concerning the examination with its attendant procedures all contribute to higher than normal readings, we feel. I believe that many of them would be considerably lower if taken 4 to 6 weeks later. Studies of blood pressure include kidney investigation, search for foci of infection, thyroid changes, eye-ground examinations, blood chemistry and Wassermann determinations.

Pericardial changes were noted in 14 cases and represented old insults to the pericardium. (One of these patients developed a large pericardial effusion after an exacerbation of an old rheumatic condition while enrolled in the University.) A history of pericardial effusion was significant, and the laboratory was of great importance in studies of these patients where our clinical findings were not conclusive.

Electrocardiographic Findings. The electrocardiogram is the least valuable of the available methods for study of heart disease in this college-age group and relatively few cases show disorders of rhythm. Friedlander⁶ has stated that 33 out of 100 rheumatic hearts revealed changes, and Stroud, Goldsmith, Polk and Thorp¹⁶ comment upon

auricular fibrillation as a terminal complication in rheumatic heart disease. Fibrillation was rare in our group. Sinus arrhythmia was noted in 87 cases but should not be regarded as a pathologic finding. The total number of electrocardiograms made was 145 and only 11 of them showed evidence of pathologic changes as auricular fibrillation, flutter, changes in *T* waves and auricular-ventricular block.

Social, Economic, Geographic and Other Influences. In view of the wide selection of students at this University, all classes of population are represented. There are a number of references in the literature as to the influence of socio-economic factors on the incidence of rheumatic heart disease. Paul and Leddy¹² at Yale showed the incidence to be 8.2 cases per 1000 in their college group, as compared to 15 per 1000 which is given as the average incidence for the same age group in other walks of life. Paul, Harrison, Salinger and DeForest,¹³ in a survey of New Haven school children, observed that social circumstances had a definite influence upon rheumatic heart disease, the poorer groups showing the greater incidence of disease.

Coleman⁵ reported on some figures given by Brewer who stated that 1 in 200 children in the group studied suffered from an active inflammation of the heart, and Richter¹⁴ states that about 2% of the 91,000 children in San Francisco are cardiac suspects. Nichol^{11a,b} showed the inequality of distribution of rheumatic heart disease in the United States and calls attention to the relative infrequency of rheumatic fever and rheumatic heart disease in Florida and sub-tropical climates.

Maddox^{10a,b} reports on a comparison of urban school groups with suburban and rural groups and notes the incidence of rheumatic heart disease to be lower in the metropolitan groups.

Levine⁹ calls attention to alteration of internal environment and our glands of internal secretion as possible factors in etiology.

The influence of climate and weather is quite evident in our therapy when we advise those with rheumatic disease to seek a warm, subtropical climate, and repeatedly warn patients against exposure to inclement weather and respiratory infections.

Summary and Conclusions. 1. A group of 28,139 students at the University of Wisconsin was given the benefit of complete physical inventory and examination at the time of their admission between 1931 and 1939, and 289 of them were found to have heart disease. Thus, the incidence of cardiac disease in this age group was 10.2 per 1000.

2. The relation of female to male heart disease was 1.7 females to 1 male, which is a higher proportion of females than is commonly observed. Congenital heart disease was reported to be present in 8 patients.

3. The mitral valve was most frequently involved and was clinically diseased in 91% of this series of cases. The next in order was

the aortic valve in 15.5% and there were only 2 cases of pulmonic valve involvement. The tricuspid valve showed no clinical evidence of disease so far as we were able to determine in our group.

4. Cardiac enlargement was shown to be present in 31.8% of the patients and 15.9% had elevated blood pressures.

5. Pericardial changes were noted in 14 cases (4.8%).

6. Disorders of rhythm, as recorded by electrocardiographic methods, were present in 11 cases (3.8%).

7. Approximately 50% of these students had the benefit of electrocardiographic and orthodiascopic investigations.

8. More of this type of material as noted by student health services should be reported in the literature in view of the similarity of circumstances and conditions surrounding the various college-age groups. It would be an additional impetus to furthering preventive medical practice.

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TREATMENT OF ADDISON'S DISEASE WITH PELLETS OF SYNTHETIC DESOXYCORTICOSTERONE ACETATE IMPLANTED SUBCUTANEOUSLY.

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RECENT reports on the use of desoxycorticosterone acetate by Thorn and Firor,⁷ McCullagh and Ryan,⁴ and Gordon³ in the treatment of Addison's disease indicate clearly the necessity for a comparative study of results of treatment with suprarenal extract, with desoxycorticosterone acetate in oil (intramuscularly) and desoxycorticosterone acetate implanted by the method of Thorn⁸ along with salt regulation. A number of cases treated by one or another of these methods has been reported.^{3,4,7,8}

This communication deals with 3 cases of Addison's disease which have been under observation for a period of from 3 to 8 years. In these cases an opportunity has been afforded to study the relative

values of cortical extract and of desoxycorticosterone acetate in oil or implanted, on the same patient.

Case Reports. *CASE 1.—History.* L. G., a married housewife, of 37, was seen first by me in April, 1937. Her chief complaints were general weakness and fatigue. She had been incapable of even mild exertion for the previous 2 to 3 years. She had noticed that her skin had gradually become brown and she had had a great deal of anorexia, nausea and occasional vomiting. In addition to the complaints of muscular asthenia, gastro-intestinal disturbances and pigmentation of the skin, the patient gave a history of bronchial asthma which started about 10 years ago in New York. She came to California 8 years ago and has had many asthmatic attacks ever since.

Physical Examination.—Physical examination revealed a rather undernourished woman, appearing extremely weak and exhausted. The patient was 4 feet 11 inches (149.9 cm.) in height and weighed only 83 pounds (37.65 kg.) at that time. Her skin showed a generalized brownish pigmentation, almost coffee-colored. There was no pigmentation of the mucous membranes. Heart sounds were of fairly good quality, there was a soft systolic apical murmur present. Blood pressure at this time was 95 systolic, 60 diastolic. Lungs were resonant, breath sounds somewhat bronchovesicular and distant with slightly prolonged respiratory phases. There was diffused tenderness over the lower abdomen. (This case is of particular interest, because of the combination of bronchial asthma and Addison's disease. It enables us to interpret the effect of the treatment upon both conditions. I mention this because some authors⁵ have advocated treatment of bronchial asthma with suprarenal extract. Others have advocated the use of potassium salts.¹)

Laboratory Data. The red blood cell count was 5,360,000, hemoglobin content 106%, and white blood cell count 9750, with 56.5% neutrophils, 27.5% lymphocytes, 6.5% eosinophils, 0.5% basophils, and 9% monocytes. The blood non-protein nitrogen level was 31 mg. per 100 cc., blood sugar 81 mg. per 100 cc., cholesterol 148 mg. per 100 cc., serum albumin 4.8%, serum globulin 2.4%. The serum sodium was 309 mg. per 100 cc., serum chlorides as NaCl 395 mg. per 100 cc., and serum potassium 24 mg. per 100 cc. The blood Wasserman reaction was negative. The basal metabolism was -15.

Roentgen Ray. Chest: A moderate hypervascularization was seen throughout both lungs. In a flat K.U.B. the kidneys were in normal position. There was no Roentgen ray evidence of calcification of the suprarenal glands.

Routine urinalysis was negative.

Treatment. The patient was placed on adrenal cortex extract, 3 cc. daily intramuscularly, and sodium chloride therapy by mouth from 10 to 20 gm. daily. The cortex extract administration was at times increased or given on alternate days, and the sodium chloride dosage adjusted according to the patient's requirements. She responded rather favorably to this treatment, but I want to stress the fact that her asthmatic attacks were not influenced at all by the cortical extract. The patient remained ambulant most of the time during the following 2 years, and maintained her weight and strength fairly well. The sodium chloride deprivation test described by Cutler, Power and Wilder² was employed as an additional aid in diagnosis in August, 1939. Treatment with desoxycorticosterone acetate in oil (Percorten* Ciba) was instituted on August 17, 1939, and continued under constant observation over a period of 4 months. During this time, dosages

* Provided by courtesy of the Ciba Pharmaceutical Products, Inc., through Dr. R. MacBrayer.

were regulated according to the method of Thorn and the optimum daily maintenance dose was determined. Through personal communication with Dr. Thorn, the pellet requirement of desoxycorticosterone acetate* for implantation was calculated from the optimum daily maintenance dose. Preparatory to implantation, as suggested by Thorn (personal communication), vital capacity and heart measurements were determined, as a precaution against possible future cardiac failure.

On December 9, 1939, 6 pellets of approximately 110 mg. each and totaling 689.8 mg. of the synthetic hormone were implanted in the infra-scapular region according to the technique of Thorn.⁸ The implantation was performed by Dr. I. Y. Oleh at the Cedars of Lebanon Hospital in Los Angeles. A graphic summary of the case over the entire period of study is given in Table 1.

CASE 2.—History. H. S., a white man of 41, an attorney, was first seen by me in November, 1937. In the previous 2 years the patient had been admitted to several hospitals for "nervous exhaustion, psychoneurosis and malnutrition." In 1931, he underwent a hernia operation. His chief complaints at the time of the examination were general weakness, loss of weight, indigestion and drowsiness.

Physical Examination. The patient was somewhat undernourished, weighing 151 pounds (68.49 kg.); height, 5 feet 8 inches (172.7 cm.). There were dark brown pigmented areas over the face, neck and shoulders. There were brown pigmented areas over both lips and over the inside of the cheeks and tongue. Blood pressure was 100 systolic, 80 diastolic. Examination of the lungs, heart and abdomen revealed no essential abnormalities.

Roentgen Ray Examination. The adrenal area revealed very dense calcifications over both sides. Intravenous urography showed these calcifications to be just above the upper pole of both kidneys. The urography also revealed a large double kidney on the left side with two sets of calyces and ureters. A Roentgen ray picture of the spine, taken in May, 1936, also showed an "area of calcification in the region of the twelfth dorsal vertebra," the significance of which apparently was overlooked. Roentgen ray examination of the chest, gall bladder and gastro-intestinal tract showed no demonstrable changes.

Laboratory Data. The Wassermann reaction was negative, urinalysis and blood count did not show any essential abnormalities. Blood urea nitrogen was 17 mg. per 100 cc., blood sugar 93 mg. per 100 cc., blood chlorides as NaCl 446 mg. per 100 cc., blood sodium 306 mg. per 100 cc. of serum, and blood potassium 27 mg. per 100 cc. of serum.

Treatment. Cortical extract and regulated salt intake were instituted on November 15, 1937, and continued until August 28, 1939. During this period of treatment, the patient kept his weight and strength fairly constant and was able to pursue his regular activities as long as he followed the prescribed regimen. On several occasions, especially during the hot season, the patient showed signs of an impending crisis, which in each instance was successfully averted by the administration of an increased dosage of the cortical extract and salt. On August 29, 1939, desoxycorticosterone acetate in oil was substituted for cortical extract with the view of determining the efficacy of implanting the crystallized hormone in this patient. This was felt advisable, since this patient was not sufficiently coöperative in following the earlier treatment and, thereby, exposed himself frequently to threatening crisis. Desoxycorticosterone acetate in oil was continued from September 12, 1939, until December 15, 1939 (3 months). During this period, the dosage of hormone and salt intake was regulated by careful observation of the patient's weight, blood pressure, maintenance of physical

* Prepared by the Ciba Pharmaceutical Products, Inc., and provided by Dr. George W. Thorn, Johns Hopkins University and Hospital.

strength and blood chemistry data. On the basis of the daily maintenance level, determined during this period, the pellet requirement was calculated. Heart measurements by orthodiagram and vital capacity were determined. On December 16, 1939, 6 pellets of about 150 mg. each, totaling 686.4 mg. of crystalline desoxycorticosterone acetate, kindly supplied by Dr. Thorn, were implanted in the infrascapular region according to the method of

TABLE 1.

Date.	Treatment.	Sodium.		Chlorides as NaCl.		Potas- sium, blood serum.	Blood sugar.	Weight, lbs.	Blood pressure, mm. Hg.
		Blood serum.	Urine.	Blood.	Urine.				
Case 1.									
April, 1938	Cortical extract and salt	309 311	..	395	..	24	81	82	90/72
May, 1938	Cortical extract and salt	339	84	95/70
Dec., 1938	Cortical extract and salt	344	24	84	88	95/70
Aug., 15-17, 1939	Cutler-Wilder test 24-hr. period	92	
	2d day salt de- privation	344	910 mg.	454	5.0 gm.	25	95/70
	4-hr. period								
	3d day salt depri- vation	329	99 mg.	429	0.8 gm.	24	90/70
Control-case	24-hr. period								
24-hr. period	2d day	336	765 mg.	413	2.5 gm.	23			
	4-hr. period								
	3d day	329	61 mg.	421	0.2 gm.	23			
Aug. 17, 1939, to Sept., 1939	Desoxycorticoster- one in oil, and salt addition	342	..	495	9.5 gm.	14.5	76	96	100/70 95/70
Dec. 9, 1939	Implantation pel- lets desoxycorticoster- one with added salt	336	..	503	..	19.1	100/70
Jan. 24, 1940	339	..	512	..	19.5	80		
May 3, 1940	331	..	495	...	23.4	80	96	110/80
Case 2.									
Nov. 15, 1937	Cortical extract and salt	306	..	446	..	27	93	151	100/80
Aug. 28, 1939	Cortical extract and salt	309	..	446	8.9 gm.	23	107	156	105/70
Aug. 29, 1939	Desoxycorticoster- one in oil, with ad- ded salt								
Sept. 12, 1939	344	..	495	6.8 gm.	19.8	91	164	112/80
Dec. 13, 1939	332	..	495	..	19.2	96		
Dec. 16, 1939	Implantation pel- lets of desoxycorti- costerone with ad- ded salt								
Feb. 4, 1940	342	..	503	..	19.8	98	168	115/90
May 8, 1940	336	..	495	..	19	96	165½	118/90

Laboratory data determined by Drs. Zeiler and Hammack and Maner Laboratory.

Dr. Thorn. The implantation was performed by Dr. I. Y. Olch at the Cedars of Lebanon Hospital in Los Angeles. A graphic summary of the case is given in Table 1. After implantation of the pellets, the desired sodium chloride intake was determined empirically by following the patient's weight and blood pressure. The optimum salt intake in Case 1 was found to be from 3 to 6 gm. daily; in Case 2 from 8 to 10 gm. daily.

CASE 3.—History. M. B., a white man of 30, was seen first in July, 1932. His past history was uneventful with the exception of occasional colds. There was no history of gonorrhea, syphilis or tuberculosis. The patient's present symptoms began in 1928 and were apparently precipitated by the repair of a rectal fistula. Following this operation, he felt weak for several months, and he noticed during this time a brownish discoloration upon his tongue and lips. A similar brownish discoloration also developed over his entire body, so much so that his friends remarked that he appeared like a colored man. In October, 1930, he was treated in a hospital for about 4 weeks. He vomited a great deal, lost weight and grew progressively weak. He did not regain some of his strength until 2 months later. During 1931, the pigmentation had increased in intensity. On July 22, 1932, the patient had a chill and temperature of 104. There was no associated cough, nasal discharge, nor pains in joints and back. The patient vomited considerably. The temperature subsided the next day, but nausea and vomiting persisted. He was admitted to the Cedars of Lebanon Hospital.

Physical Examination. Patient seemed acutely ill and was quite weak and drowsy. He had a peculiar type of air hunger. Pupils reacted to light and accommodation, tongue was coated, and there were bluish-black patches of pigmentation upon tongue, buccal mucous membranes and gums. Neck: left lobe of thyroid gland somewhat enlarged. Heart was not enlarged, there were no murmurs and no irregularities present. Lungs: resonant throughout, no râles. Abdomen: liver and spleen not palpable. Skin: showed diffuse brownish pigmentation with scattered patches of deeper pigmentation, especially dark over face, nipples, penis, scrotum and hands. Temperature 97, pulse 80, blood pressure 100 systolic, 70 diastolic.

Laboratory Examination. Urinalysis normal, except for positive acetone and diacetic acid. Blood count on admission: hemoglobin 107%, red blood cell count 6,200,000, white cell count 4000, with neutrophils 41%, lymphocytes 53.5%, transitionals and large mononuclears 5.5%. Five days later, after treatment had begun, hemoglobin was 97%, the red blood cell count 5,900,000, the white cell count 6900, with 47% neutrophils, 47.5% lymphocytes, transitionals and large mononuclears 4% and eosinophils 1.5%. Blood Wassermann reaction negative, blood sugar 83 mg. per 100 cc., non-protein nitrogen 33 mg. per 100 cc., Van den Bergh reaction normal. Basal metabolism -16. Test meal showed free hydrochloric acid of 12 and total acidity of 18.

Treatment. The patient was placed on Eschatin, 5 cc. daily, given intravenously and intramuscularly at first, and later 2 to 4 cc. daily intramuscularly. The most striking effect was the immediate relief of the gastric discomfort, cessation of nausea and vomiting, and the return and increase of appetite within the first few days. Not less striking, but somewhat slower was the remarkable influence on the asthenia. Improvement in strength and well being followed within a few days. The improvement in strength was not accompanied by an appreciable change in blood pressure. After being on a dosage of 2 to 4 cc. daily for a few weeks, the patient was able to follow his daily routine of life. In December, 1932, I referred the patient to the Mayo Clinic for confirmation of the diagnosis and treatment, where he was under the care of Dr. A. M. Snell. Physical and laboratory examination there gave no additional information, except a skin biopsy, which showed markedly increased melanin pigment in the basal cell layer of the skin. He was advised to continue the small doses of Eschatin, and in addition, to take sodium chloride, 10 to 15 gm. daily. Since then, the patient has led a normal life. There have been times when he has had a respiratory infection. At these times, his gastro-intestinal symptoms and asthenia would recur, his blood pressure would vary slightly, and increased doses of Eschatin, and sodium chloride were neces-

sary to control these symptoms. Subsequent examination at the Mayo Clinic in June, 1936, revealed his blood pressure to be 100 systolic and 60 diastolic. Roentgenograms of the suprarenal glands and of the thorax showed nothing of significance. The blood urea reading was 30 mg., chlorides 578, sodium 347, and potassium 20.9 for each 100 cc. of blood. As additional treatment at this time, he was instructed in a low potassium diet to be supplemented with 8 gm. of sodium chloride and 4 gm. of sodium citrate daily. It was not felt necessary for him to use injections of cortical hormone, except in emergencies. The patient has been under observation for 8 years. His weight has increased gradually from 132 to 143 pounds, his blood pressure and pigmentation have changed little. Throughout these years, he has carried on successfully in his business, which has taken him on many trips.

This case is thought to represent the latent, or stationary, type of Addison's disease. It seems probable that there must be some functional reserve so far as the adrenal cortex is concerned, or he would not have progressed so satisfactorily.

Case 3 represents successful continuous treatment with cortical extract and salt administration for a period of 8 years, and with the duration of the disease for 12 years. The survival time in this case is one of the longest reported in the literature.⁶

In review, Case 1 was treated from May, 1937, to August, 1939, with cortical extract and regulated salt intake, and from August, 1939, to December, 1939 (4 months), with desoxycorticosterone in oil, and from December, 1939, onwards with implanted desoxycorticosterone acetate pellets (8 months).

Case 2 was treated from November, 1937, to August, 1939, with cortical extract and regulated salt intake, from August, 1939, to December, 1939 (4 months), with desoxycorticosterone acetate, and from December, 1939, onwards with implanted desoxycorticosterone acetate pellets (8 months).

Case 3 has been under treatment since 1932. Since it was possible to maintain this patient in good condition by means of cortical extract and regulated salt intake administration, no change of treatment was attempted.

Cases 1 and 2, who had been restored to some degree of health by treatment with cortical extract and salt administration for the past 3 years, are, at present, 9 months after subcutaneous implantation of the synthetic hormone pellets, able to attend to their duties regularly, and are leading a life of moderately restricted activity. The synthetic hormone implantation resulted in a definite increase in weight and improvement of muscular strength and well being. Tendency to edema was controlled by a reduction of the salt intake. The average requirement of sodium chloride was about one-third of the amount necessary under the cortical extract treatment. The blood pressure, both the systolic and diastolic, was considerably higher under the synthetic hormone treatment. An appreciable decrease of pigmentation was noted in both cases after implantation. The laboratory examinations resulted in a definite increase of the

blood, sodium and chloride levels, and in a marked decrease of the potassium level.

No local or systemic complications followed the implantation of the synthetic hormone pellets.

Summary. Two patients with Addison's disease who had been treated from 2 to 3 years with cortical extract injections and salt by mouth were placed on desoxycorticosterone acetate in oil. After the daily quantity of this substance necessary for satisfactory maintenance had been determined, these patients were subsequently implanted with pellets of crystalline desoxycorticosterone acetate. The implantation of pellets of the synthetic hormone resulted in a gain of body weight, an increase in blood pressure, general physical improvement and return to normal activity. Clinical improvement was associated with a normalization of the blood electrolyte relationship during 10 months of observation.

One patient with Addison's disease was treated over a period of 8 years with cortical extract injections and large doses of salt by mouth. No change of treatment was attempted in this case since this patient's symptoms were adequately controlled in this way.

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THE LOCAL USE OF SULFANILAMIDE POWDER AND HYDROGEN PEROXIDE IN WOUND INFECTIONS.

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THERE are only a few reports in the literature dealing with the efficacy of sulfanilamide used locally, even though it has been widely employed systemically. Jensen, Johnson and Nelson⁸ used it locally in 39 cases of compound fractures as a prophylactic with excellent results. They found that with careful hemostasis, thorough débridement, and primary closure, the introduction of 5 to 15 gm. of powdered sulfanilamide could eliminate complicating infections which were formerly observed in 27% of these cases. They also observed that the sulfanilamide was absorbed readily from the wound, and produced blood concentrations approximating those produced by oral administration. It remains a moot question whether the effect was due to the local concentration of the drug,

to the substance carried to the inflamed tissues *via* the blood stream, or a combination of the two.

Sezary¹⁸ has reported better results with chancroid lesions by the local application of sulfanilamide than by oral administration. Dentists have also reported success in using the drug locally in dry sockets¹⁹ and also in root canal therapy.¹

Lockwood and Lynch¹³ as well as Larson, Bieter, Levine and Hoyt¹¹ suggest that even small amounts of peptone may greatly reduce the bacteriostatic and bacteriocidal effect of sulfanilamide and its derivatives. King and Henschel¹⁰ found that tissue fragments interfered with the bacteriostatic effect of sulfanilamide on beta streptococci *in vitro*. In the light of these two findings, the wounds in the cases to be described were washed out thoroughly with hydrogen peroxide until they presented a clean appearance. The fact that no beta streptococci could be cultured from either case 16 hours after powdered sulfanilamide had been placed in the wounds indicated that the remaining peptone and tissue fragments, in all likelihood, were insufficient to interfere with adequate bacteriostasis.

Fox⁷ found that increased oxygen availability increased the bacteriostatic action of sulfanilamide, whereas reducing agents decreased its effect. Main, Shinn and Mellon¹⁵ showed that sulfanilamide has an anticalase activity which prevents the destruction of the hydrogen peroxide produced by the organisms. This allows the hydrogen peroxide to reach a high enough concentration to prove toxic to the organisms. Mellon, Locke and Shinn¹⁷ give added support to the oxidative-enzymatic theory of the mode of action of sulfanilamide. They find that the free amino group of sulfanilamide when incompletely oxidized is responsible for the anticalase activity exhibited by the drug. The fact that the streptococcus, pneumococcus, gonococcus, meningococcus and *B. coli* organisms all produce hydrogen peroxide is given as the reason for the wide therapeutic applicability of the drug. They suggest that staphylococcic lesions are usually of a reducing nature and do not allow for the oxidation of sulfanilamide to products that exhibit anti-enzymatic activity. It is to be noted that the staphylococci were eradicated with greater difficulty than the streptococci in our cases. It is felt that the hydrogen peroxide helped to overcome the reducing properties present in the wounds.

In view of the above findings, hydrogen peroxide was left in the wounds in our cases, and powdered sulfanilamide suspended in hydrogen peroxide was introduced into the sinuses leading from these wounds. Hydrogen peroxide was used as the oxidizing agent of choice because it was suspected of being the intermediate agent responsible for the toxicity of sulfanilamide to the bacteria.¹⁵ In this manner oxygen availability was increased and the toxic effect of the sulfanilamide on the offending bacteria was potentiated. In

support of this we have some experiments *in vitro* by Fox.^{7b} He found that the resultant bacteriostasis produced by the addition of small amounts of hydrogen peroxide to cultures of *strep. hemolyticus* containing 10 mg. of sulfanilamide per 100 cc. of media was more than ten times greater than the bacteriostasis produced by corresponding amounts of sulfanilamide used alone and more than two hundred times greater than that produced by equal quantities of hydrogen peroxide used alone.

The total amount of sulfanilamide which would usually be given by mouth in 24 hours was placed in the wound at one time, and this was replenished daily. Thorough cleansing allowed intimate contact with the absorbing surface. All recesses and sinuses were flushed with the suspension of sulfanilamide in hydrogen peroxide. Lawrence¹² reported a case of chronic undermining streptococcal ulcer using a total of 8400 gr. of sulfanilamide orally to obtain a cure. In our case of a similar type with more extensive involvement we used a total of only 570 gr. locally.

Because of the high blood sulfanilamide concentrations resulting from this mode of administration, all of the toxic manifestations produced by oral administration may also be expected here. It is possible that high local concentrations may prove toxic to the tissues. However, no ill effect was noted locally in either of the 2 cases presented. In the case of chronic periostitis it is of interest to note that the patient developed an alopecia of the scalp which proved transient. She also developed a papulovesicular rash of the palms of both hands and the soles of both feet. Both of these toxic symptoms are a general manifestation of the drug. Local areas of alopecia in rats receiving sulfanilamide over long periods of time have been observed by Antopol, Goldman and Sampson.²

Bricker and Graham⁴ found a delay in healing of abdominal wounds in dogs receiving sulfanilamide by mouth. Key and Burford⁹ found that experimental fractures of the forelegs of rabbits healed just as well with sulfanilamide in the wound as without it. In our cases healing continued at a rapid pace at a time when the wound was thoroughly saturated with sulfanilamide.

Many modifications suggest themselves. It is possible that the local use of sulfanilamide with zinc peroxide might prove efficacious in the treatment of chronic undermining ulcers due to the micro-aërophilic hemolytic streptococcus, one of the organisms present in Case 1. Meleney and Harvey¹⁵ found that the combination of zinc peroxide used locally and sulfanilamide orally was more effective in such cases than either alone. The possibility also suggests itself that it might be an effective treatment for acute and chronic osteomyelitis. The organisms encountered in our 2 cases are similar to those found in osteomyelitis. Besides, as can be seen in the accompanying illustrations, complete healing of the osteoperiostitis ultimately was achieved.

Case Reports. CASE 1.—R. N., a 16-year-old white female was first admitted, April 9, 1938, for a soft tissue swelling at the lower end of the right thigh, which on later admissions proved to be an abscess resulting from a chronic periostitis. She was admitted 5 times during the next 2 years, spending a total of 26 weeks in the hospital. Wound cultures on those occasions revealed hemolytic streptococci. Treatment consisted in curetting the bone and incising the abscesses, but always she returned with new collections of pus and other sinuses.

Present Admission. September 27, 1939, to June 7, 1940.

Chief Complaint. Pain along inner aspect of right thigh, 2 weeks' duration. Fever of a few days' duration.

Physical Examination. Grayish-brown discharge from sinuses of right thigh. Otherwise negative.

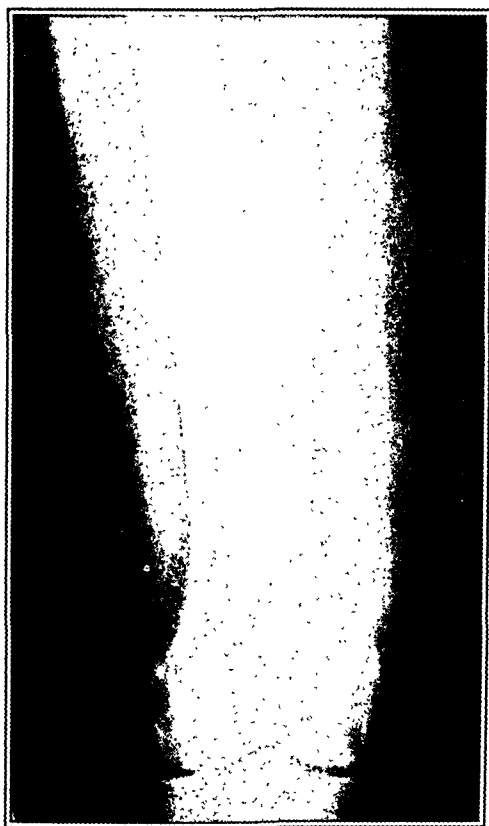


FIG. 1.—Case 1. February 10, 1939. Lower end of right femur showing early periostitis.

Laboratory. Temperature, 103°. Roentgen rays: Periostitis with cortical necrosis, reported by Dr. N. J. Furst, Chief Roentgenologist. Wound culture: *Staph. aureus hemolyticus*, *Strep. hemolyticus* of the micro-aërophilic type.

Course. Over a period of 10 weeks various forms of treatment were tried unsuccessfully. The yellowish-gray discharge became more profuse and the sinus tracts deepened. On December 14, 1939, an operation was performed in which the sinus tracts were widely excised, the bone curetted and a through and through rubber drain was placed between the lower end of the femur and the hamstring muscles.

Immediately after operation her temperature rose sharply to 105° and a tremendous greenish yellow purulent discharge poured out of the wound. Dakin's tubes were inserted and continuous irrigation with azochloramide, 1 to 3300, was accomplished through them. The skin flaps became very tender, there was marked itching of the entire leg and in less than 2 weeks the skin became undermined to within 2 inches of Poupart's ligament. At this time the wound extended for three-quarters of the length of the thigh. Wound culture on January 4, 1940, showed *Staph. aureus* and *Strep. hemolyticus*. Three days later, a severe hemorrhage from one of the sinus tracts caused the patient to go into shock. A transfusion was given and the tract

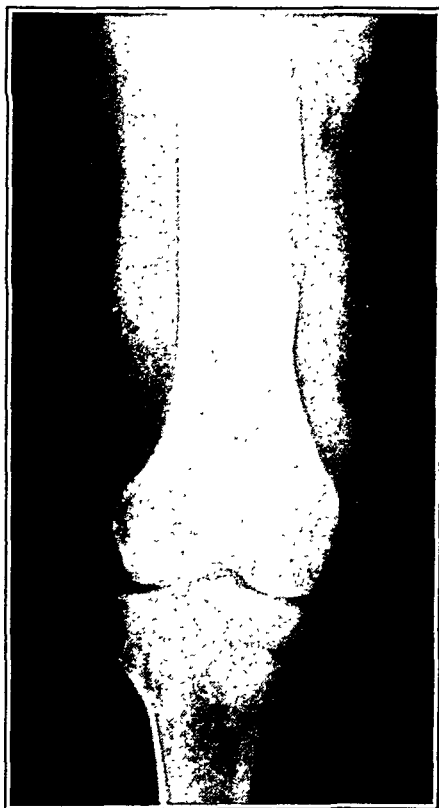


FIG. 2.—Case 1. October 10, 1939. Same, showing osteoperiostitis 4 months before institution of local sulfanilamide and hydrogen peroxide therapy.

packed tightly. At this time, azochloramide was discontinued and gentian violet, 5%, was used in the wound in its stead. During the next month, she had 3 other exsanguinating hemorrhages. At the time of the last hemorrhage she became unconscious and her respirations became Cheyne-Stokes in character. Shortly afterwards foot drop and toe drop developed, along with marked edema of the entire extremity from the knee down. Metastatic sinuses developed about the heel and ankle. One of these caused an area about 3 inches long and 1 inch wide to sluff away, exposing the upper part of the tendon of Achilles. In addition to the other organisms previously encountered, *B. pyocyaneus* was now cultured from the wounds of the thigh and ankle. Acetic acid, 1%, used continually for 1 week failed to diminish the effect of this organism.

On February 17, 1940, after the wound had been thoroughly cleansed and flushed with hydrogen peroxide and under sterile technique, sulfanilamide powder (4 gm.) was packed under the skin flap and placed on the granulations. Sulfanilamide powder (2 gm.) was suspended in 30 cc. of hydrogen peroxide and this suspension was introduced into the sinuses. Many gauze dressings were used to cover the wound. In 24 hours the granulations appeared healthy for the first time, the discharge became about one-fourth of what it previously had been, and the tenderness had disappeared. This treatment was repeated for 4 days in succession in the



FIG. 3.—Case 1. May 20, 1940. Same, showing healing osteoperiostitis 3 months following local sulfanilamide and hydrogen peroxide therapy.

wound on the thigh. But slight improvement was noted in the draining sinus at the ankle. Cultures from it were still positive for all the organisms as before, whereas those from the thigh were only positive for *B. pyocyaneus*. When the above treatment was applied to the ankle wound, it too improved. Since that time, in spite of the presence of *B. pyocyaneus*, the wounds steadily healed and the sinuses closed. Cultures remained consistently negative for all organisms except *B. pyocyaneus* until the wound had completely healed.

Two untoward symptoms were noted. The hair on the patient's head began to fall out. While this was alarming for a short time, it soon ceased. She also developed a papulo-vesicular eruption of the palms and soles of both hands and feet. This slowly disappeared over a period of a month, during which time no sulfanilamide was used.

During the last few days of February, the discharge became more profuse and *B. pyocyaneus* was again found to be the offending organism. On February 29, 1940, 6 gm. of powdered sulfanilamide were again introduced after the wound had been thoroughly cleansed with hydrogen peroxide. Within 48 hours the discharge became about one-tenth of what it previously had been. Repetition of the wound cultures at that time revealed that the causative organism was still present, but it appears that some inhibition of its growth had taken place. Blood and urine sulfanilamide determinations were made 16 hours following the above administration of 6 gm. of powdered sulfanilamide, and it was found that the free sulfanilamide in the

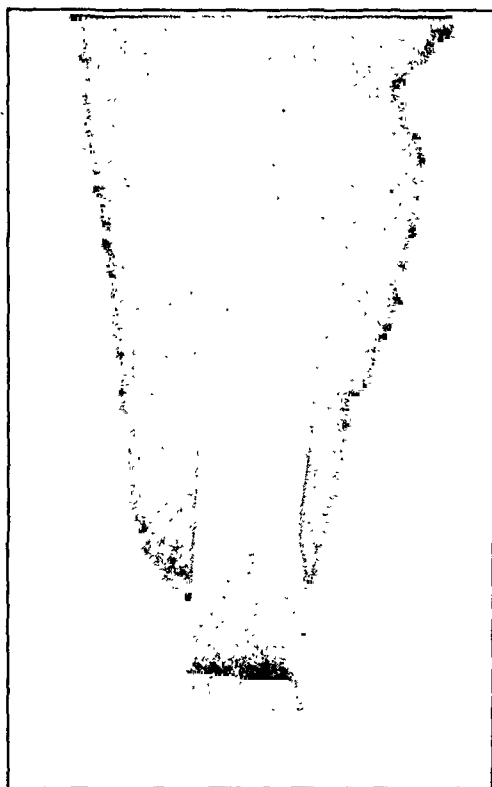


FIG. 4.—Case 1. August 1, 1940. Same, showing complete healing of osteoperiostitic process with complete filling in of all osteoporotic areas.

blood was 5.4 mg. per 100 cc., and the total was 10.2 mg. per 100 cc. Forty hours later the free sulfanilamide in the blood was 2.4 mg. per 100 cc. and the total 4.6 mg. per 100 cc. On March 24, 1940, 4 gm. of sulfanilamide powder were introduced into the wound at a time when it was one-third of its former size. A blood concentration of free sulfanilamide of 1.5 mg. per 100 cc. was found to be present after 16 hours. At 40 hours 0.4 mg. per 100 cc. of free sulfanilamide was found to be present. Four days later 4 gm. of sulfanilamide powder were reinserted and similar blood concentration levels were recorded.

Once a week powdered sulfanilamide was sprayed on the wound by means of a Shelanski insufflator. After each treatment the discharge became noticeably less and the wound gradually closed. By the end of May complete healing had taken place and the patient began walking with the aid of a cane. She was discharged June 7, 1940. A Roentgen ray taken August 1, 1940, revealed complete healing of the osteoperiostitis (Fig. 4).

CASE 2.—H. D., a 19-year-old white male, was admitted March 14, 1940; discharged, April 4, 1940.

Chief Complaint. Infection above right knee following trauma of 1 week's duration.

Physical Examination. Thick brown purulent discharge coming from an opening in suprapatellar region of right leg. The leg was held in a fixed position and there was marked tenderness and spasticity of the muscles of the thigh. The femoral glands were slightly enlarged and tender.

Laboratory. Wound culture: *Staph. aureus hemolyticus* and *Strep. hemolyticus*. Roentgen ray: Negative for bone lesions. Temperature, 101.4°.

Course. After hot wet dressings the temperature subsided. However, the discharge became more profuse and the pain in the thigh became more intense. Because of the lack of improvement in the symptoms, the decision was reached to open the abscess. Eight days following admission, a large intramuscular abscess was incised and packed with 6 gm. of sulfanilamide powder after some hydrogen peroxide had been left in the wound. The following day 4 gm. of sulfanilamide powder, along with hydrogen peroxide, was placed in the wound. Two days following this hemorrhage from a few subcutaneous bleeders took place. These were controlled by ligation. Three days following the original introduction of the sulfanilamide the discharge had ceased completely. Cultures from the depths of the cavity revealed the presence of *Staph. aureus hemolyticus*. Cultures repeated 2 days later were found to be sterile. The wound was brought together with windowed adhesive. The inguinal and femoral adenitis slowly subsided. Twelve days after operation the patient was discharged with the wound healing well by primary union. Free sulfanilamide was found to be present in the blood for 82 hours following its original introduction on successive days. The highest concentration reached was 1.6 mg. per 100 cc. A total of but 10 gm. of powdered sulfanilamide was used.

Summary. 1. Two cases of wound infection with *Strep. hemolyticus* and *Staph. aureus hemolyticus* were treated successfully by repeated local administration of powdered sulfanilamide and hydrogen peroxide.

2. In Case 1 where concomitant bone involvement was present, complete healing of the osteoperiostitis took place.

The author wishes to express his gratitude to Dr. William Antopol, Pathologist and Director of Laboratories, for his sincere advice and criticisms; to Dr. Max Danzis and Dr. Eugene V. Parsonnet for permission to use Case 1; to Dr. Bernard H. Greenfield for permission to use Case 2; and to Dr. N. J. Furst for his Roentgen interpretations.

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THE INTRAVENOUS USE OF SODIUM SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA AND PNEUMOCOCCUS INFECTIONS.*

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IN the treatment of pneumonia and pneumococcic infections with sulfapyridine, the oral administration is to be preferred. There are times, however, when for one reason or another the administration by a route other than oral is desirable. This is especially true with those patients who are seriously ill or who are unable to take oral medication. It also applies to those who have not responded satisfactorily to sulfapyridine orally or who cannot be given serum. In such cases an effective concentration of sulfapyridine in the blood may be obtained immediately by the use of sodium sulfapyridine intravenously. It is our purpose in this paper to emphasize the practical importance of this route of administration in the treatment of severe pneumococcic infections and to point out that the advantages are greater than the disadvantages.

Selection of Cases. The material for this study consists of work done on 80 patients with pneumonia selected from a total of 200 admitted to Cook County Hospital between November, 1939, and May, 1940. Their selection was made on the basis of the greater severity of their illness at the time of admission to the service or because they failed to respond to oral sulfapyridine. The causative agent was the pneumococcus in 73 patients, the streptococcus in 3, the *B. Friedländer* in 2, and the etiology was not determined in the remaining 2. Four patients had meningitis caused by the pneumococcus. A summary of the 80 patients treated is shown in Table 1.

* This study has been made possible through the coöperative efforts of the attending faculty at Cook County Hospital.

TABLE 1.—ANALYSIS OF CASES.

	Total.		Coma delirium.		Bacteremia.		Relapse.		Oral S.P. failure.	
	No.	Died.	No.	Died.	No.	Died.	No.	Died.	No.	Died.
Total	80	22*	24	19	37	17	4	0	13	1
Pneumococcus	73	17	19	15	34	14	4	0	13	1
Streptococcus	3	2	3	2	2	2	0	0	0	0
B. Friedländer	2	1	0	0	1	1	0	0	0	0
Unclassified	2	2	2	2	0	0	0	0	0	0

During the past year all patients with pneumonia were given oral sulfapyridine routinely on admission or as soon as the clinical diagnosis was established. In the above group sodium sulfapyridine was used intravenously supplementary to oral sulfapyridine in all except 5 patients who were treated by the intravenous route alone (oral medication was omitted). A total of 115 injections were used. It was not given to patients with a mild or moderately severe pneumonia, or to those who responded to oral sulfapyridine. However, no restrictions were put on its use in critical cases. Often a patient showed signs of a preëxisting disease, or of a complication associated with the pneumonia at the time of admission to the hospital. This added to the gravity of the prognosis. We were aware of the potential toxicity of sodium sulfapyridine, but decided that urgency for treatment of the infection was more important than the possible toxic effect of the drug. Control of the more recent superimposed pneumonia seemed to offer the best chance for recovery. As a result it was used in: (a) all patients who appeared terminal with little or no chance of recovery; (b) patients whose temperature did not show an appreciable decline within 24 hours after the administration of oral sulfapyridine (Chart 2); (c) patients who failed to obtain a level of 4 to 5 mg. per 100 cc. within 24 hours unless the temperature and pulse had returned to normal (Chart 3); (d) patients who, because of nausea and vomiting, could not retain, or refused to take oral sulfapyridine (Chart 2, *A* and *B*); (e) patients who, after an initial favorable response, had a relapse in spite of continued full dosage of oral sulfapyridine (Chart 3, *A*, *B*, *C*); (f) patients with a persistent bacteremia.

Methods. All patients in this series were given sodium sulfapyridine† intravenously; the dose, from 3 to 5 gm., was dissolved just before use in from 50 to 100 cc. of 0.8% solution of sodium chloride or distilled water just below boiling point. It was administered in 10 to 30 minutes, depending chiefly on whether or not the patient was receiving intravenous fluids at the time. When such was the case the solution was injected into the tubing of the infusion or was mixed with the fluid in the infusion flask. When no infusion was being given (approximately one-half the cases) the solution was injected directly into the antecubital vein at a rate of from 5 to 10 cc. per minute. Free sulfapyridine blood levels were determined

* Fifteen patients died within the first 24 hours (see Table 3).

† The sodium sulfapyridine used in this study was made available through the generosity of Merck & Co.

at various intervals after each injection (2 to 12 hours). In 3 patients sulfapyridine levels of the gastric juice were made simultaneously with blood determinations (see Table 2).

TABLE 2.—SULFAPYRIDINE LEVELS OF GASTRIC CONTENTS AND BLOOD AFTER 4 GRAMS OF SODIUM SULFAPYRIDINE INTRAVENOUSLY.

	Before I.V.	5 min.	10 min.	30 min.	60 min.	2 hr.	12 hr.	24 hr.
Case 1 (J. D.):								
Gastric—Free	0	12.5	22.2	23.8	19.6	20.0	8.7	
Total	0	12.8	22.2	23.8	19.6	20.8	9.6	
Blood—Free	0	5.2	2.8	0.7	
Total	0	5.7	3.6	1.8	
Case 2 (H. R.):*								
Gastric—Free	100-0*	24.7	37.0	18.2	5.0	2.9	..	13.5
Total	100-0	25.0	38.0	..	5.0	3.3	..	16.6
Blood—Free	2.27	11.7	7.8	..	16.4
Total	3.2	11.7	9.5	..	21.0
Case 3 (J. G.):								
Gastric—Free	0	4.2	4.2	4.8	6.4	5.9	4.4	
Total	0	4.2	5.0	5.7	6.4	6.3	4.7	
Blood—Free	0	9.8	7.6	7.6	3.5	
Total	0	9.8	9.1	..	5.8	

Cases 1 and 2 had nausea and vomiting. Case 3 had no nausea and vomiting.

* Four grams of sulfapyridine were given orally 12 hours before the intravenous salt was administered. The stomach was lavaged until the washings were free of sulfapyridine. Then sodium sulfapyridine was injected.

Toxic Manifestations. No severe toxic reaction was encountered during or after administration of a solution of sodium sulfapyridine. No chills, extreme restlessness, apnea, fall in blood pressure, collapse, muscle-twitching or convulsions occurred. A few patients complained of a mild burning sensation along the course of the vein in the arm. Such symptoms, however, are not uncommon with intravenous medications that are strongly alkaline.

Thrombophlebitis or perivascular reactions were not encountered.

In very toxic or delirious patients sodium sulfapyridine seemed to aggravate the symptoms temporarily, just as did oral sulfapyridine. The incidence of blood dyscrasia or renal damage was no higher in patients who received the intravenous salt than in those who received the oral salt alone.

Of the 80 patients treated, nausea and vomiting occurred in 15; nausea alone in 5 additional cases.

Five patients were treated with intravenous sodium sulfapyridine alone. Each received an injection of 4 gm. at 12- to 24-hour intervals until a satisfactory response was noted. One patient received three injections, 3 received four, and 1 received five. All recovered from their pneumonia. Nausea and vomiting occurred after the first injection in 4 patients. However, after subsequent injections it was mild and of little consequence. Nausea, then, was the chief complaint. In 3 patients who were treated in this manner (Table 2), simultaneous blood and gastric concentrations of free and total sulfapyridine were determined at frequent intervals. The gastric levels in 2 patients (Cases 1 and 2) who experienced nausea and

vomiting were from 2 to 4 times the simultaneous blood levels. This was most marked in the first 30 minutes after the injection and corresponded with the period when nausea and vomiting were most pronounced. With the patient (Case 3) who did not experience nausea and vomiting, the gastric concentration never approximated that in the blood. We were able, also, to confirm the observations of Kinsman³ that gastric lavage relieved the nausea. The early investigators⁵ attributed nausea and vomiting after oral sulfapyridine to gastric irritation, but because it came on so rapidly after injection of sodium sulfapyridine, central irritation was

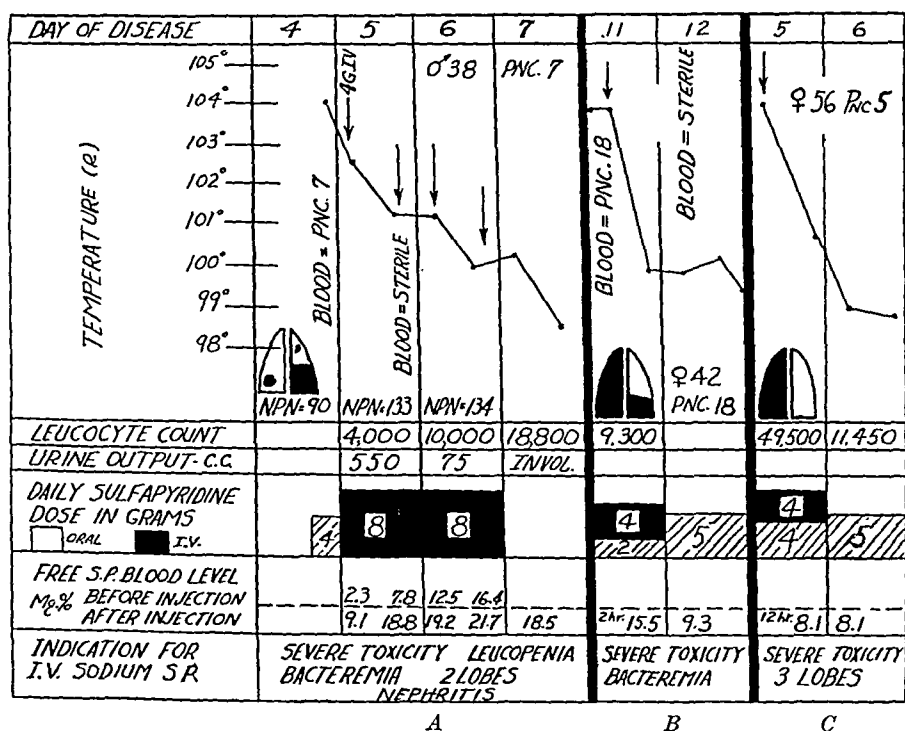


CHART 1.

thought⁴ to be a likely explanation. In this series, the onset of nausea and vomiting, however, was not sufficiently rapid to be attributable to irritation of the central nervous system. Further, the fact that the concentration of sulfapyridine in the gastric contents was higher than the level in the blood within a few minutes of the injection suggested that gastric irritation played a part in the production of nausea and vomiting. These observations are in accord with those of Finland¹ who pointed out "... local gastric irritation may be an important contributing factor in the nausea and vomiting, irrespective of any possible central effect of the drug." Haviland and Blake² made similar observations on vomitus of patients receiving parenteral sulfapyridine. The findings in Case 2

suggest that the concentration of sulfapyridine in the stomach contents is many times higher after oral sulfapyridine than after intravenous sodium sulfapyridine alone. Nevertheless, the sulfapyridine blood levels are higher and the clinical response more dramatic in the latter. It appears, therefore, that there is less likelihood of nausea and vomiting after sodium sulfapyridine intravenously than after oral sulfapyridine. The danger of other toxic reactions probably is no greater, and the response to treatment more immediate and certain.

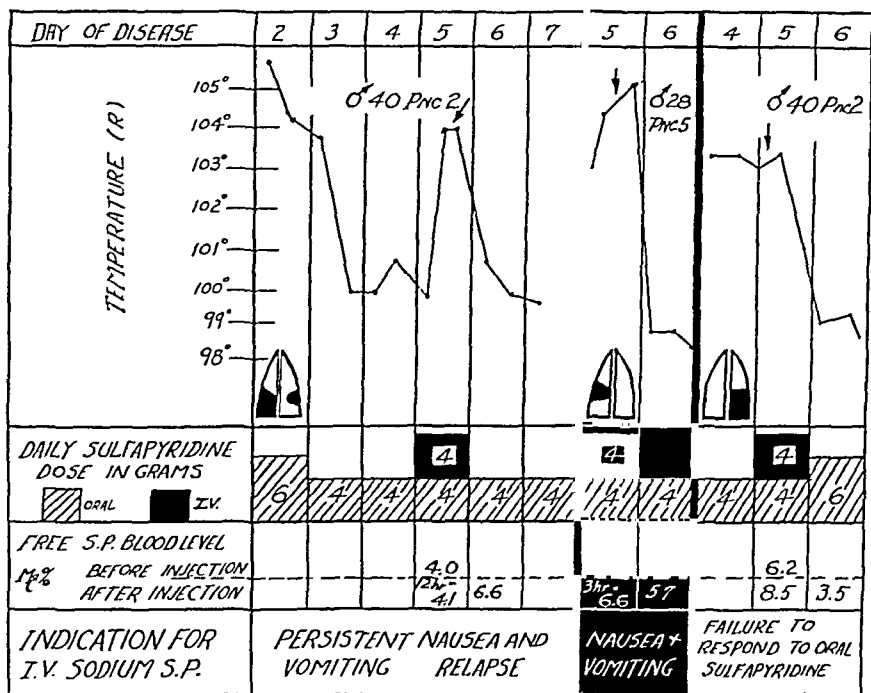


CHART 2.

Results (Table 1). Patients who were in coma or delirium when first examined were usually unable to take sulfapyridine orally. In such patients the bacteriologic diagnosis often could not be made in less than 12 hours and for this reason serotherapy could not be considered. There were 24 patients who were comatose or delirious at the time of admission. All appeared moribund. Intravenous sodium sulfapyridine was given in each instance, and 5 recovered.

The following is a summary of an illustrative case: H. R. (Chart 1, A), male, aged 38 years, was admitted to the hospital in a semi-comatose state. He was able to take only the initial dose of sulfapyridine orally. He had an involvement of two lobes and a bacteremia. He also had an impending uremia and acidosis as shown by the blood chemistry (non-protein nitrogen 90 mg., creatinine 5.1 mg., CO₂

36 vol. %). Nausea and vomiting were persistent. Oliguria was present and became marked in 24 hours. Subsequently the blood non-protein nitrogen rose to 134 mg. White blood count on admission was 4000; 3 days later it had risen to 18,000. Intravenous sodium sulfapyridine together with sufficient glucose and fluid was given every 12 hours for 4 days. The patient became rational, coöperative and recovered from his pneumonia. The volume output of urine returned to normal, but the specific gravity remained low. The uremic state responded slowly. It was felt the nitrogen retention was the result of a previous nephritis, of which he gave a history, plus the superimposed pneumococcus infection, rather than a toxic manifestation of sulfapyridine.

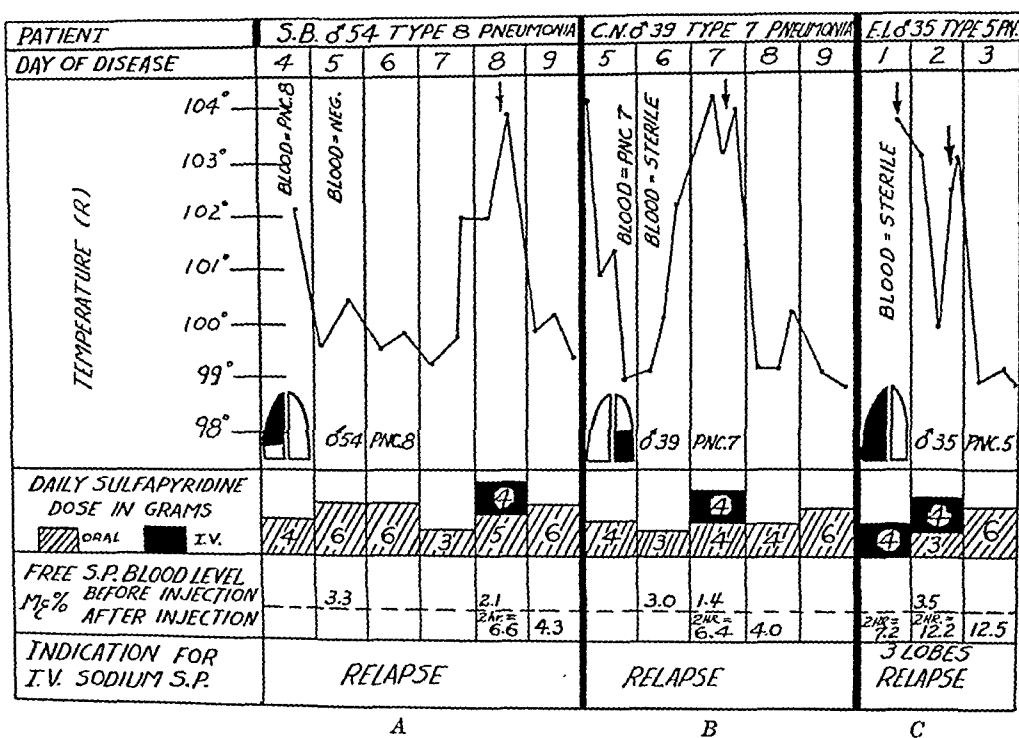


CHART 3.

Bacteremia was present in 37 of the 80 patients; 17 died, a mortality of 46%. In view of the type of cases that are often admitted to this hospital and that comprised this group, we feel this has some significance. Treatment was almost always delayed until after the fourth day of the disease.

In 4 patients showing a good initial response to oral sulfapyridine there occurred a recrudescence of the clinical signs and symptoms, indicating a reactivation or spread of their infection. Two of these patients had bacteremia. This occurred in the presence of inadequate blood levels (less than 5 mg. per 100 cc.) and before active

immunity had developed. In each instance intravenous administration of the sodium sulfapyridine brought about a favorable clinical response (see Charts 2A, 3A, B, C).

In 13 patients adequate oral dosage of sulfapyridine failed to bring about a decline in temperature and pulse within 24 hours. In some cases this was in spite of the fact the blood level was 5 mg. per 100 cc. or more. However, in all but 1 case prompt recovery followed the intravenous administration of sodium sulfapyridine.

Of the 75 patients treated with intravenous sodium sulfapyridine supplementary to oral sulfapyridine, 22 died (Tables 1 and 3). Fifteen died within 24 hours after admission to the hospital; 7 survived from 1 to 10 days (Table 3). Of these, 4 received serum

TABLE 3.—ANALYSIS OF DEATHS.

Case No.	Death.	Day of ill.	Age decade.	Etiology.	No. of injections.	I.V. S.P.	Oral S.P.	S.P. blood level.	Findings on first examination.
1	4 hrs.	5	6	Unc.	1	4.0	0	0	2 lobes; coma
2	4 hrs.	5	6	Pnc.	1	4.0	0	0	Meningitis
3	6 hrs.	5	5	II*	1	4.0	Yes	12.5	Pul. edema; semicoma
4	6 hrs.	2	3	Hemo-* Strep.	1	4.0	Yes	0	Benzol poisoning; aplastic anemia; semicoma
5	6 hrs.	7	6	II*	1	4.0	0	7.7	Coma; pul. edema
6	6 hrs.	5	6	II*	1	4.0	Yes	6.4	Pul. edema; 3 lobes
7	8 hrs.	4	6	VIII*	1	4.0	Yes	5.4	Semicoma; alcoholism
8	12 hrs.	5	6	I	1	4.0	Yes	8.3	Stuporous
9	12 hrs.	5	6	V*	1	4.0	Yes	0	Pul. edema; 2 lobes; arterio-sclerosis
10	12 hrs.	5	6	II*	1	4.0	Yes	0	Coma; 3 lobes; pul. edema
11	12 hrs.	5	5	XXXIII*	1	4.0	Yes	0	Semicoma; 3 lobes; pul. edema
12	18 hrs.	2	3	B. Fried.*	1	4.0	Yes	5.7	
13	24 hrs.	7	6	Unc.	1	4.0	Yes	7.1	Coma; 3 lobes
14	24 hrs.	7	3	Pnc.	2	8.0	Yes	0	Broncho-pleural fistula; bronchiectasis; empyema; semicoma; tuberculosis
15	24 hrs.	7	3	II*†	2	8.0	Yes	9.2	Coma; 2 lobes
16	30 hrs.	4	1	Hemo-* Strep.	2	3.0	Yes	25.0	Empyema; semicoma
17	30 hrs.	5	3	XXVIII*†	2	8.0	Yes	10.0	Meningitis
18	2 days	5	5	III*†	1	4.0	Yes	5.0	Anaphylaxis (see text)
19	4 days	4	4	II*†	2	8.0	Yes	9.0	Oral sulfapyridine failure (see text)
20	5 days	3	6	I*	1	4.0	Yes	12.5	Thyrototoxicosis; aur. fib.; 2 lobes
21	10 days	6	6	II*	-1	4.0	0	62.5	Nephritis; uremia; jaundice; lung abscesses
22	10 days	5	5	II*†	2	8.0	Yes	10.8	Delirium tremens; multiple lobes

* Bacteremia.

† Serum was used in treatment.

Pnc. = pneumococcus no type. Unc. = no bacteriologic diagnosis made; I, II, etc. = pneumococcus type. S.P. = sulfapyridine.

therapy in addition to chemotherapy. One patient (Case 18) died from anaphylactic shock during the administration of serum. One patient (Case 17) who had pneumococcus meningitis and lobar pneumonia died 30 hours after entrance to the hospital. The 2 other patients who received serum (Cases 19 and 22) had Type II bacteremia and multiple lobe involvement. A patient (Case 21) in the sixth decade, who survived 10 days, had Type II pneumococcus pneumonia with bacteremia complicated by chronic nephritis with uremia, jaundice, and multiple lung abscesses. A child (Case 16),

8 years of age, developed pneumonia and empyema following scarlet fever. He was given intravenous sodium sulfapyridine before the bacteriologic diagnosis of hemolytic streptococcus was made. Bacteremia was present in 17 patients. Sixteen of the 22 fatal cases were admitted on the fifth day of their illness or later. The remaining 6 (Cases 4, 7, 12, 16, 19, 20) had an overwhelming infection on admission from which recovery could scarcely be hoped for. In all cases where blood concentrations of free sulfapyridine were determined, the levels (5.4–62.5 mg. per 100 cc.) were above those usually considered to be effective (5 mg. per 100 cc.).

Comment. Sodium sulfapyridine is a valuable addition to the armamentarium of the physician treating pneumonia and one that he should constantly keep in mind. It should not be used to replace oral sulfapyridine, the value of which has been so amply recorded during the last 2 years. However, there are times when parenteral administration is desirable and it is then that the sodium salt is of value. Patients who are unable to have serum, or who are unable to retain the drug orally because of nausea and vomiting, or who are unable to cooperate because of coma or delirium, are candidates for sodium sulfapyridine intravenously. It was given upon admission and followed by oral sulfapyridine in many of our patients whose condition appeared serious enough to warrant its use. The value of a sufficiently high blood concentration of sulfapyridine should not be overlooked in the treatment of the seriously ill patient. The presence of preëxisting disease or a complication of pneumonia made us feel that an effective blood concentration of sulfapyridine was imperative for best results. Also, it should be pointed out that all but 1 of 13 patients who failed to respond to oral sulfapyridine and 4 patients who had experienced a relapse made a prompt favorable response after sodium sulfapyridine was given intravenously. The high incidence of death in this series is readily explained by the fact that only those cases with a grave prognosis were selected for treatment with intravenous sodium sulfapyridine.

It is true that accidents may follow the intravenous use of sodium sulfapyridine, but in our experience these may be avoided by careful preparation and administration of the solution.

We wish to emphasize the benefits that may be derived from the intravenous use of sodium sulfapyridine in patients seriously ill with pneumonia and stress the importance of its therapeutic use alone, or in conjunction with oral sulfapyridine.

Conclusions. 1. No severe toxic reactions were seen during or following 115 intravenous injections of sodium sulfapyridine.

2. Response to treatment is more immediate with intravenous sodium sulfapyridine than with oral sulfapyridine.

3. Repeated at 12-hour intervals a dose of 0.06 gm. per kilo maintains a level of from 6 to 15 mg. per 100 cc.

4. The concentration of sulfapyridine in the stomach contents

probably produces sufficient gastric irritation to play an important part in the production of nausea and vomiting.

5. Intravenous sodium sulfapyridine is a valuable agent in critical patients when an immediate effective blood level is desired.

6. Fear of reactions following the intravenous administration of sodium sulfapyridine seems unwarranted and should not limit its more general application.

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ACCURACY OF FLUOROSCOPY IN THE DETECTION OF PULMONARY TUBERCULOSIS.

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FLUOROSCOPY continues to be widely employed for the detection of pulmonary tuberculosis, despite recent developments in other low-cost methods of Roentgen ray examination. The obvious disadvantage of fluoroscopic examination is the absence of a permanent record that may be reviewed by others or used for comparison in serial examinations. Nevertheless, the inexpensiveness of the method has resulted in its extensive use in diagnostic practice as well as in group examinations.

Studies estimating the accuracy of fluoroscopy as compared with conventional celluloid film examination have given widely divergent results. Investigations made prior to the introduction of the Patterson "B" screen showed gross inaccuracy in the detection of minimal and moderately advanced tuberculosis.² A study made at this Institute in 1932 indicated that apical infiltrations extending below the clavicle were in most instances detected, but tuberculous infiltrations limited to the lung field above the clavicle were seldom recognizable by fluoroscopic examination.⁶

More recent experience with the improved Patterson "B" screen has indicated a higher degree of accuracy for fluoroscopic examination.^{1,5,8} Although some recent comparative studies have included large numbers of subjects,^{4,8} they have been confined to student and employee groups in which the prevalence of tuberculous abnormalities is small.

Fluoroscopic examination has been used at this Institute since 1933 as a routine procedure in the study of new patients and in the periodic reëxamination of contacts as a screen to select persons for film examination. It seemed desirable to determine the accuracy of the method as used in the routine practice of the clinic; and to ascertain as well the limits of its accuracy in the detection of smaller lesions sought in epidemiologic studies.

This study includes 1021 duplicate fluoroscopic and film examinations made from June, 1938, to May, 1940. It seemed expedient to limit film examination to contacts, because in a limited series this should provide a larger number of tuberculous abnormalities, and because a film record of these patients was desired for the purposes of other investigations. In addition, duplicate examinations were given other patients in whom the routine fluoroscopic study suggested the presence of abnormalities.

The examining physicians were classed for purposes of comparison in three groups: 1, those having special training in roentgenologic interpretation and long experience in fluoroscopy; 2, staff physicians having considerable experience in fluoroscopy, but with limited or no special training in roentgenologic interpretation; and 3, fellows and graduate students receiving short periods of training.

Effort was made to obtain an unequivocal report from the fluoroscopic physician. Indiscriminate "suspicion" of abnormalities was discouraged. Physicians were directed to classify abnormalities as "definite," "probable" (suspected), or "possible" (slightly suspected).

Detection of Active Parenchymal Tuberculosis. Forty-eight of the 1021 patients had easily recognizable gross pleural abnormalities or non-tuberculous pulmonary or mediastinal diseases which made them unsuitable for the purpose of the present study. This group, which has been excluded from further consideration, was comprised of pleural effusion (15 patients), atypical pneumonia (14 patients), pulmonary abscess (4 patients), aneurysm (2 patients), residual lipiodol (2 patients), pneumatocele (2 patients), sarcoidosis (2 patients), silicosis (2 patients) and single instances of bronchiectasis, bronchogenic carcinoma, lymphoblastoma, pleural calcification, and substernal thyroid gland enlargement.

The remaining 973 patients have been classified into three groups, according to whether the presence of significant pulmonary infiltrations was considered by the fluoroscopist to be definite, probable, or unlikely (Table 1). Infiltrations were thought to be absent or unlikely in 692 patients; in 668 instances (96.6%) this diagnosis was confirmed by film examination. The presence of a tuberculous infiltration was thought to be definite on fluoroscopic examination in 246 patients; in 237 instances (96.7%) this diagnosis was confirmed. In the other 35 patients infiltrations were thought probably to be present; film examination revealed definite lesions in 10 (28.6%).

TABLE 1.—DETECTION OF ACTIVE PARENCHYMAL TUBERCULOSIS BY FLUOROSCOPY.

Physician.	Experience.*	No. of duplicate examinations.	Excluded (non-tbc. lesions).	Lesion absent or improbable.		Lesion probable, fluoroscopy.	Lesion definite, film.	Lesion definite.	
				Fluor- oscopy.	Film.			Fluor- oscopy.	Film.
A	Group I	150	5	96	96	4	1	45	44
B		142	2	115	113	2	1	23	22
C	Group II	170	12	100	97	12	3	46	45
D		95	2	66	65	1	0	26	25
E		89	9	53	49	3	1	24	24
F		70	5	47	41	1	1	17	17
G	Group III	62	1	40	37	2	2	19	19
H		57	2	44	43	2	0	9	7
I		38	2	27	25	2	0	7	7
J		37	4	24	23	1	1	8	8
K		35	1	32	31	0	0	2	2
L		26	2	13	13	3	0	8	6
M		23	0	19	19	1	0	5	5
N		9	1	3	3	0	0	5	5
O		7	0	7	7	0	0	0	0
P		6	0	4	4	0	0	2	2
Q		3	0	1	1	0	0	2	2
R		2	0	1	1	1	0	0	0
Total	...	1021	48	692	668 (96.6%)	35	10 (28.6%)	246	237 (96.7%)

* Classification described on p 225.

It is evident that individual variations in accuracy occurred but were relatively slight. Experienced physicians of Group I were approximately 99% accurate in excluding tuberculosis, while physicians in Group II were 94.9% accurate, and the least experienced physicians of Group III were 97.3% accurate.

Reinfection Type Tuberculosis. Far-advanced tuberculosis was present in 116 patients (Table 2). All of these appeared to the fluoroscopist as definite infiltrations.

TABLE 2.—ACCURACY OF DETECTION OF REINFECTION-TYPE TUBERCULOSIS BY FLUOROSCOPY.

Extent.	Number found by film examination.	Fluoroscopic report.			
		Lesion definite.	Lesion probable.	Lesion possible.	Negative.
Far advanced	116	116	0	0	0
Moderately advanced	52	51	0	0	1
Minimal:					
a. Treatment advised	43	37	3	1	2
b. Observation advised	36	13	5	11	7
Apical pleuritis	40	10	0	5	25

Moderately advanced tuberculosis was present in 52 patients. In 51 instances the lesions were definite on fluoroscopic examination. One patient, reported as negative on fluoroscopic examination, was

given film examination a week later because of suggestive symptoms, and moderately advanced tuberculosis was found. Reëxamination by another fluoroscopist clearly revealed the lesion.

Minimal tuberculosis was present in 79 patients. These have been subdivided into two groups, the first comprising patients whose lesions were sufficiently marked to warrant reporting to the Board of Health and to require immediate treatment. The second group comprised patients with smaller infiltrations, usually confined to the lung field above the clavicles, of questionable clinical significance. Continued observation was the customary recommendation for patients with these small apical infiltrations. Minimal lesions requiring treatment were present in 43 patients. In 37 instances the infiltrations appeared definite to the fluoroscopist; in 3 instances the presence of an infiltration was suspected; in 1 instance possible infiltration was reported; and in 2 instances the fluoroscopist failed to detect the abnormality. Smaller minimal lesions, for which observation was advised, were present in 36 patients. In 13 instances the infiltrations appeared definite; in 5 instances the presence of a lesion was suspected; in 11 instances possible infiltration was described, and in 7 instances the fluoroscopic report was negative.

Projections of thickened pleura at the extreme apex, presumably representing obsolete tuberculous foci and considered to be merely of epidemiologic significance, were present in 40 patients. Only in 10 instances did these scars appear as definite lesions on fluoroscopic examination; in 5 instances possible lesions were described; and in the remaining 25 instances no abnormality was noted by the fluoroscopist.

Tracheobronchial Lymph Node Tuberculosis. Definite tracheobronchial lymph node enlargement, presumably due to caseous tuberculosis, was reported on fluoroscopic examination of 22 patients (Table 3). In 18 instances the same diagnosis was reported on film examination. Tracheobronchial lymph node enlargement was considered probable in 40 patients. Film examination showed definite enlargement in only 8 of these patients.

TABLE 3.—ACCURACY OF DETECTION OF TUBERCULOUS TRACHEOBRONCHIAL LYMPH NODE ENLARGEMENT BY FLUOROSCOPY.

Fluoroscopy: Lesion definite	22
Confirmed by film examination	18
Fluoroscopy: Lesion probable	40
Lesion definite on film examination	8

Three additional patients were found on film examination to have enlarged tuberculous tracheobronchial lymph nodes. In one instance possible enlargement was described by the fluoroscopist, and in two instances the fluoroscopic report was negative.

A total of 29 cases of tracheobronchial lymph node enlargement was found on film examination of the entire group. On fluoroscopic examination, as noted above, 18 had appeared definite and 8 prob-

able. Possible lymph node enlargement was described in 1 patient, and in 2 the fluoroscopic report was negative.

Calcified Primary Tuberculosis. Calcified foci in the lungs and tracheobronchial lymph nodes are identified in Roentgen ray films by their density, irregularity in outline, sharply defined margins and not infrequently by their position or site in the lung field. It is often necessary to take films in rotated positions or with over-exposed technique in order to make certain that the shadows are due to calcium deposition and not to blood-vessels. Since these lesions are not regarded as clinically significant, no attempt was made in the present study to determine their incidence accurately by rotation films. Fluoroscopy has the advantage of permitting the operator to rotate the patient and thus differentiate shadows of vessels from calcified foci. For this reason a density due to calcium may be seen on fluoroscopy but not recognized as such in the Roentgen ray film. On the other hand, since these lesions are so much less important than pulmonary infiltrations, fluoroscopists are unlikely to make as careful a search for their presence. These factors are presumably responsible for the divergent results obtained by fluoroscopic and film examination in the present study.

The presence of tracheobronchial lymph node calcification or of a calcified peripheral nodule was described as definite on fluoroscopic examination in 105 patients (Table 4). The same diagnosis was made on film examination in 82 instances. Probable calcified primary lesions were reported in 14 patients. Definite calcification was reported on film examination in 8 of these patients.

TABLE 4.—ACCURACY OF DETECTION OF CALCIFIED PRIMARY LESIONS BY FLUOROSCOPY.

Type of lesion.	Number diagnosed on film examination.	Fluoroscopic report.			
		Lesion defi- nite.	Lesion prob- able.	Lesion pos- sible.	Nega- tive.
Peripheral nodule	50	28	2	0	20
Tracheobronchial node	64	35	3	1	25
Complex	29	19	3	0	7

In 105 patients a calcified primary lesion appeared definite on fluoroscopy; the lesion appeared definite on film examination in 82 instances.

In 14 patients a calcified primary lesion appeared probable on fluoroscopy; film examination showed a definite lesion in 8 of these patients.

A total of 143 calcified primary lesions was reported on film examination. These lesions appeared definite to the fluoroscopist in 82 instances, probable in 8 instances, and possible in 1 instance. In 52 instances no calcification was reported by the fluoroscopist. Table 4 indicates that the discrepancies in diagnosis between fluoroscopic and film examination were equally marked in the case of peripheral nodules and in the case of tracheobronchial calcifications. More consistent results were obtained when both components of the primary complex were present.

Obesity. It is generally believed that fluoroscopy is unsatisfactory for the examination of obese adults. In the present study, the fluoroscopist noted in 31 instances that examination was not entirely satisfactory because of marked obesity. Mediastinal lymph node enlargement due to lymphoblastoma was detected in 1 of these patients. The fluoroscopist reported tuberculous infiltration in 2 patients; in 1 patient, film examination failed to confirm the diagnosis, while in the other, it showed minimal tuberculosis. In the remaining 28 patients fluoroscopic examination was reported as negative for tuberculosis. This diagnosis was confirmed in 27 instances. The single lesion missed was a small minimal apical infiltration of questionable clinical significance.

This series, although small, suggests that fluoroscopic examination even in the obese will detect tuberculous infiltrations of immediate clinical significance.

Fluoroscopy in Children. One hundred and twenty-nine of the duplicate examinations reported in this series were made in children less than 13 years of age. The majority of these were aged 4 to 12 years, since fluoroscopic examination was rarely attempted in infants. Advanced tuberculosis with cavity was found in a negro child of 4 years. A pleural effusion was detected in 1 white child. Apical tuberculosis of minimal extent was found in a negro girl of 12 years. Infiltration was suspected in a 5-year-old negro child; film examination demonstrated miliary tuberculosis.

Fluoroscopic examination was reported negative in 74 children; film examination confirmed this diagnosis in every instance. Active primary type tuberculosis was considered definite on fluoroscopic examination of 23 children. In 14 instances the same diagnosis was made on film examination, and in 2 instances a diagnosis of suspected tuberculosis was made. In 28 children the presence of active primary type tuberculosis was considered probable on fluoroscopic examination. In only 3 of these children was a definite diagnosis of tuberculosis made on film examination. It is noteworthy that in 12 children the same diagnosis of probable tuberculous tracheobronchial lymph node was made on fluoroscopic and film examination.

Calcified primary lesions appeared probable or definite on fluoroscopy in 10 children. Calcification appeared definite on film examination in 8 of these children. Nine other children in whom calcification was not suspected on fluoroscopic examination were diagnosed as having calcified primary lesions on film examination.

Individual Variations in Accuracy. Fluoroscopic examinations made by 18 physicians are included in this study. Individual variations in accuracy were not marked (Table 1). Nevertheless, it appears significant that 2 physicians were responsible for the 4 instances in which infiltrations of immediate clinical significance were missed by fluoroscopic examination. One of these physicians

had had considerable experience in fluoroscopy and was receiving special training in chest roentgenology. The other physician had had relatively little roentgenological experience.

Dark adaptation studies were made to determine whether the individual variations might be due to poor dark adaptation caused by vitamin A deficiency or to some interference with the scotopic mechanism in the eye. Twelve staff physicians were examined with the Hecht dark adaptometer, through the kindness of Dr. Robb McDonald, of the Department of Ophthalmology in the School of Medicine of the University of Pennsylvania. No significant abnormality was found in any of the physicians.

Further study was directed toward determining the relative visual acuity of the various physicians as measured by ability to define under the fluoroscope the orientation of small slits made in discs after intervals of dark adaptation of 2, 5 and 8 minutes. Although a method satisfactory for quantitative comparison was not developed, preliminary studies confirmed the finding of Chantraine and Cramer⁸ that considerable variation exists in the relative visual acuity of individual physicians as tested by this method.

It seems reasonable to conclude that failure to wait for adequate dark adaptation was responsible for the occasional gross inaccuracies rather than lack of training or limitations of the fluoroscope. Smaller supraclavicular lesions, on the other hand, were frequently overlooked by physicians who had not had special training in film interpretation. Such small lesions would probably have been disregarded by these men on films as well as on fluoroscopic examination. In a number of patients, however, small lesions of this type are not recognized even on careful examination by experienced physicians; these instances indicate that fluoroscopic examination cannot be relied upon for the detection of the earliest lesions of pulmonary tuberculosis. This finding is in accord with Hedvall's conclusion.⁷

Discussion. Duplicate fluoroscopic and film examinations given 1021 patients who had history of respiratory symptoms or history of exposure to tuberculosis, indicate that in clinical practice fluoroscopy provides an accurate method for the detection of pulmonary tuberculosis. Abnormalities appeared definite or probable to the fluoroscopist in 329 of these patients; of the remaining 692 patients in whom no definite abnormality was reported on fluoroscopic examination, only 4 (0.6%) had tuberculous lesions of immediate clinical significance. Fluoroscopy was less satisfactory in the detection of smaller apical infiltrations that would be merely observed or disregarded by the clinician, although of great interest to the epidemiologist. In 18 instances in this series, fluoroscopic examination failed to detect these small but not necessarily obsolete minimal apical lesions which represent, as Hedvall⁷ has shown, the earliest roentgenologic evidence of pulmonary tuberculosis. As far as the use of

fluoroscopy in clinical practice is concerned, however, it is only fair to state that lesions of the type described by Hedvall are demonstrable only on films made with superior technique, and are at present overlooked by the majority of roentgenologists and disregarded by most clinicians.

Stiehm⁸ has reported several instances in which significant infiltrations detected by fluoroscopic examination were so hidden by superimposed bony structures that they were not detected on single film examination. Although no instance of this occurred in the present series, 2 such cases have recently been encountered in a study of the development of tuberculosis in nursing students. Infiltrations have been found on fluoroscopic examination of 2 students in whose films, taken at another institution, no certain abnormality could be distinguished.

The accuracy with which tuberculous infiltrations can be detected in children is even greater, as might be expected from their easier radiability and the lesser prevalence of small supraclavicular lesions in children. Duplicate examinations given 125 children less than 13 years of age revealed no instance in which a tuberculous infiltration was overlooked on fluoroscopic examination.

Tuberculous tracheobronchial lymph node enlargement, definite on film examination, was detected in all but 2 instances by fluoroscopy. As a rule, when lymph node enlargement was definite on one method of examination, it appeared definite on the other; when probable on one method of examination, it appeared probable on the other. It is questionable whether film or fluoroscopic examination is the more authoritative in the diagnosis of tuberculous lymph node enlargement.

It is similarly questionable which is the more accurate method for the diagnosis of calcified primary lesions. In a considerable number of patients in this study calcification appeared definite on fluoroscopy, while flat film examination showed no abnormality that would warrant a definite diagnosis of calcified tuberculosis. An even larger proportion of patients diagnosed as having a calcified primary lesion on flat film examination was considered negative on fluoroscopy. The discrepancies were so great that diagnoses of calcified primary tuberculosis made on fluoroscopic examination alone or on flat film examination alone must be regarded with a measure of skepticism.

Conclusions. 1. Fluoroscopic examination by physicians with limited training and experience in fluoroscopy should detect in diagnostic practice or in mass surveys almost all tuberculous infiltrations of immediate clinical significance. In the present series of approximately 1000 duplicate examinations, in only 4 instances were significant lesions of this type not recognized. Results satisfactory for clinical purposes were obtained even in obese patients.

2. Smaller tuberculous lesions of questionable clinical significance,

but of considerable importance in epidemiologic investigations, were frequently overlooked by physicians without special training in roentgenologic interpretation. In most instances physicians who had special training and experience were able to detect even these minute lesions.

3. Individual variations in accuracy among the group of 18 physicians studied were not correlated with vitamin A deficiency or local changes that might cause poor dark adaptation. It seemed probable that failure to wait for adequate dark adaptation was the chief factor responsible for poor results.

4. An especially high degree of accuracy was observed in the fluoroscopic examination of children.

5. The results of fluoroscopic and film examination in the diagnosis of tuberculous tracheobronchial lymph node enlargement corresponded closely.

6. Rather inconsistent results were given by fluoroscopy and by flat film examination in the diagnosis of calcified primary lesions. Which of the methods is the more accurate is not proven.

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SPONDYLARTHROSIS ANKYLOPOIETICA.

A REVIEW AND REPORT OF TWENTY CASES.

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ALTHOUGH spondylarthrosis ankylopoietica has long been recognized as a clinical and pathologic entity, it is our belief that there still exists some confusion about it among internists in general. It seems useful, therefore, to report the 20 cases studied by us and to review more extensively than has been done in the American medical literature the development of the present concept of the disease. The European literature, particularly the German, has from time to time contained excellent discussions of the subject, notably by Simmonds,⁷¹ Fraenkel,^{19a,b} Proebster,⁵⁸ Krebs,^{38a} and Ehrlich.^{15c} In this country important papers by the late Dr. Joseph L. Miller^{53a,b} should be mentioned.

Spondylarthritis ankylopoietica is a chronic, progressive, probably infectious disease of the vertebral column and adjacent structures, occurring chiefly in young adult males, and characterized clinically by pain and stiffness in the back, with or without involvement of the hip and shoulder joints. There is early ankylosis of the small posterior intervertebral articulations and of the sacro-iliac joints, along with marked atrophy of the vertebral bodies. The costochondral joints may become ankylosed. Calcification of the longitudinal ligaments of the spine may take place producing the so-called "bamboo spine." The disease is subject to exacerbation and remission and the changes described in the spine may progress in the absence of pain.

Material. Among the 2395 patients registered at the Desert Sanatorium prior to January 1, 1936, there were diagnosed 228 cases of atrophic arthritis, 115 cases of hypertrophic arthritis, and 42 of "spondylitis." Among the case records of patients suffering from "spondylitis," with or without other joint disease, roentgenograms were available for study in 36 instances, and we were able to make a diagnosis of spondylarthritis ankylopoietica in 20 of these. The records of those patients not actually seen by the present authors were carefully reviewed. The material from the 20 cases of spondylarthritis ankylopoietica has been collected in Table 1. References will be made later in this paper to an unpublished statistical study of the complete records of 201 cases of atrophic arthritis and 95 cases of hypertrophic arthritis.

Historical.—Previous to 1893, cases of primary rigidity of the spine had excited little special interest and were classified as "spondylitis deformans." In that year Bechterew^{5a} published a paper in which he described what he believed was a new neurologic disease, characterized by stiffness of all or part of the spine, a kyphosis involving chiefly the upper thoracic spine, paresis of the muscles of the neck, back, and extremities, atrophy of the shoulder girdle and of the back muscles, reduced skin sensitivity over the areas supplied by the cervical and other spinal nerves, and finally prominent symptoms of root irritation. Bechterew described in detail the cases of 2 female patients, both in the sixth decade of life, with symptoms of 2 and 5 years' duration. A third case was that of a young male patient 39 years old, who had suffered from the disease for 10 years. Bechterew stated that the man was suffering from a much more severe illness than were the women. In the same paper Bechterew included brief notes on 2 patients seen by him some years previously. Both of these were elderly males. He postulated that a diffuse ankylosing process in the spine was associated with an inflammation of the epidural sheaths, and that heredity and trauma were the chief factors in initiating this condition. In 1897 Bechterew^{5b} reported another case which he believed belonged in the same group.

In the same year (1897) Strümpell⁷⁷ described the case of a 39-year-old male who during the previous 4 years had gradually developed ankylosis of the spine and of the hip joints. In this case there was no question of a senile kyphosis. Strümpell also included notes on 2 other similar patients previously seen by him. Both of these were young adult males. The following year, 1898, Pierre Marie,⁴⁸ presented in detail 3 cases of rigid spine occurring in males all of whom placed the onset of their illness in the fourth

Roentgenographic findings.										Clinical findings and history.																	
Patient.	Case number.	Age of onset.	Duration in years.	Period of observation.	Posterior articulations.	Calcification of longitudinal ligaments.	Narrowing of intervertebral spaces.	Sacro-iliac joints.	Ischia.	Pubes.	Iliac crests.	Hip joints.	Shoulder joints.	Peripheral joints.	Sedimentation rate.	W.B.C. in thous.	Fever.	Hemoglobin, %.	Serum calcium.	Serum phosphorus.	Urine.	Conditions associated with onset.	Chronic diseases.	Acute episodes.	Rheumatic fever.	Scarlet fever.	Family history of joint disease.
K.J.	484	23	3	3 mos.	+	-	-	4+	+	+	+	+	+	+	+	9-10	+	96	...	1-2 W.B.C.	Splenomegaly Eosinophilia Lymphadenopathy Mitral valve	5 yrs.		
R.Q.	3060	21	3½	18 mos.	2+	-	2+	4+	+	2+	+	+	+	+	+	9.4	+	105	...	Occ. W.B.C.	Sacro-iliac strain	Iritis	...	10 yrs.			
R.W.	723	26	4	5 yrs.	4+	3+	2+	4+	+	2+	+	+	+	+	+	9.9	+	103	10.1/3.5	Occ. W.B.C.	Pulmonary tube. Pericarditis Pneumonitis	Iritis	..			
E.H.	888	24	4	7 yrs.	4+	3+	2+	4+	+	2+	+	+	+	+	+	9.0	+	100	...	Occ. W.B.C.		Iritis	..			
R.C.R.	297	23	4½	1 yr.	4+	3+	+	4+	2+	2+	-	2+	+	+	+	10.8	-	80	10.6/	-	Parotissillar abscess	Otitis					
I.G.	236	24	5	3 mos.	4+	3+	-	4+	3+	3+	3+	2+	+	+	+	8.4	+	90	9.5/3.9	Occ. W.B.C.	Iritis					
W.M.C.	332	18	6	6 yrs.	4+	4+	3+	4+	4+	2+	4+	2+	+	+	+	6.8	+	92	...	Occ. W.B.C.	Polyarthritits or rheumatic fever	Aene vulgaris	Iritis				
M.M.	2803	27	7	3 yrs.	4+	4+	-	4+	2+	3+	4+	2+	+	+	+	11.8	+	88	...	Occ. W.B.C.	Ischiorectal abscess	Iritis Pneumonia	..		+	
O.R.	1042	27	7½	1 wk.	4+	3+	+	4+	4+	+	2+	2+	+	+	+	10.6	+	65	...	10-15 W.B.C.	Pulmonary tube.			
J.C.	417	27	8	4 mos.	4+	-	+	4+	+	+	+	+	+	+	+	9.0	+	38	...	5-10 W.B.C.	Acute G.C.	Chronic bronchitis Pulmonary tube. fatal	Thyrototoxicosis	..			
W.J.	719	21	8	9 mos.	4+	4+	+	4+	+	+	+	+	+	+	+	10.6	+	81	...	2-3 W.B.C.	Trauma to spine		Thyrototoxicosis	..			
W.R.S.	4	26	11	9 mos.	4+	4+	+	+	+	+	+	+	+	+	+	14.2	+	80	...	Occ. R.B.C. Bacillurea		Thyrototoxicosis	..			
B.W.	2079	21	11	4 yrs.	4+	2+	-	+	+	+	+	+	+	+	+	14.8	+	93	...	3-30 R.B.C.	Spontaneous pneumothorax		+	
W.K.	665	24	11	1 wk.	2+	+	-	3+	+	+	+	2+	+	+	+	13.7	+	83	...	Occ. W.B.C.	Fistula-in-ano	Coronary disease			
M.O.	575	36	13	10 mos.	4+	4+	3+	4+	2+	+	2+	2+	+	+	+	11.3	+	105	...	10-20 W.B.C.	War exposure				
E.G.	2177	20	15½	10 mos.	4+	4+	2+	4+	2+	+	2+	2+	+	+	+	11.3	+	105	...	10-20 W.B.C.	War exposure				
M.K.	2749	18	14	1 day	4+	4+	3+	4+	4+	+	+	3+	+	+	+	8.2	+	100	9.6/	-	Pulmonary tube.	Renal colic Iritis	..		+	
H.M.	554	40	15	2 yrs.	4+	4+	3+	4+	4+	2+	2+	+	+	+	+	13.4	+	77	9.8/4.3	Occ. W.B.C.	Typhoid	Pericarditis Pneumonia with empyema	..	26 yrs.		
W.B.	86	33	20	5 mos.	4+	4+	3+	4+	4+	4+	+	+	+	+	+	8.8	+	80	...	1-3 W.B.C.	Chronic G.C. Scarlet fever		18 yrs.			
R.C.	940	26	24	3 mos.	4+	4+	+	4+	4+	4+	4+	2+	+	+	+	14.2	-	91	...	Occ. W.B.C.							

decade of life. He also included in this paper notes on 2 other cases of his own and on Strümpell's case. He felt that this group of 6 cases represented a clinical entity characterized by complete fusion of the dorsal and lumbar spine, associated with a more or less pronounced ankylosis of the shoulder and hip joints, and without involvement of the small joints of the extremities. Marie⁴⁹ asserted that these cases were distinct from the one which he and Astié had reported in 1897, the latter being similar to the cases described by Bechterew. As none of his patients had come to autopsy Marie described in detail and illustrated in his text a skeleton from Dupuytren's collection, which he felt represented what would be found in a case of "Spondylose Rhizomélisque." This skeleton presented the picture that we now know is characteristic of spondylarthrosis ankylopoietica. Such spines had been observed and described before (Gurlt,²⁹ Braun⁷), but for the most part were not clearly differentiated from those with "Spondylitis Deformans" (hypertrophic arthritis of the spine). According to Buckley,⁹ typical skeletons had been described by Connor in 1700 and by Hilton Fagge in 1877. V. Leyden⁴⁵ clearly described the two pathologic types, but classified them both as "Spondylitis Deformans." Marsh⁵¹ in 1895 gave a particularly clear description of such a spine, pointing out the calcification of the longitudinal ligaments, and the absence of any decrease in the intervertebral spaces. Marie, however, was the first to correlate the clinical picture of spondylarthrosis ankylopoietica and the anatomic changes present in the spine.

In 1899 Bechterew⁵⁰ reviewed his earlier cases and reported 2 of "Strümpell's Disease" in males. Bechterew again asserted his belief that he had described a distinct clinical entity.^{5d} He emphasized the occurrence of kyphosis in his disease as opposed to an abnormal straightness of the spine in the cases reported by Strümpell and Marie. He^{5d,e} reported the findings at autopsy on one of his male patients who had died of pneumonia. There was a dorsal kyphosis. Osteophytes were noted on the thoracic vertebræ, along with complete or partial fusion of most of the dorsal vertebræ. The intervertebral spaces were much reduced, especially in the regions where the vertebræ had grown together. The above description makes it likely that he was dealing with an advanced case of hypertrophic arthritis of the spine with kyphosis. Certainly here was no new neurologic disease.

In the same year Marie and Léri⁵⁰ presented the autopsy findings in the case of a patient who had suffered from "Spondylose Rhizomélisque." The striking feature was the great involvement of the posterior articulations of the spine, most of which were completely ankylosed. There was no calcification of the anterior or posterior common ligaments.

Articles appeared early in the American literature. Dana¹³ presented a thorough discussion of it. Goldwaith²⁶ recognized two forms of arthritis of the spine, osteo-arthritis and rheumatoid arthritis, but he seems to have fallen into the error, still common, of confusing advanced cases of spondylarthrosis ankylopoietica with hypertrophic arthritis of the spine. Elliot¹⁶ in 1905 pleaded for more pathologic studies of these cases and less speculation. He reported the autopsy findings in 1 case.

Between 1898 and 1904 innumerable papers were published on the subject. They consisted chiefly of case reports accompanied by conjectures about the etiology and pathology of rigid spine (Schultze,⁶⁷ Popoff,⁶⁶ Schataloff,⁶³ Sängér,⁶¹ Jacobian and Beckman,³² Hoffman,³¹ Damsch,¹² Bregman,⁸ Müller,⁶⁴ Galliard,²² Kudrjaschoff,⁴⁰ Anschütz,¹ and Magnus-Levy⁴⁷). With neither pathologic nor roentgenographic evidence to support their views these authors did little to clarify the situation.

In 1899 Valentini⁵³ published an important paper describing 2 patients who had had symptoms for 10 years. In 1 case roentgenograms had been made and showed what is commonly termed "bamboo spine." In the same year Méry⁵² reported a case of rigid spine in a man 38 years old. Symptoms

had been present for only 3 years. The roentgenograms made in this case showed no evidence of "bamboo spine." Méry observed, however, that there was no narrowing of the intervertebral spaces.

In 1900 Heiligenthal³⁰ assembled the records of most of the cases reported up to that time and summarized them in tabular form with a full bibliography. He attempted, not altogether successfully, to separate the cases into two groups, those resembling the cases reported by Strümpell and Marie, and those characteristic of "Bechterew's Disease." About this time Senator⁷⁰ and Schlesinger⁷⁵ published reviews on the pathology of ankylosing processes involving the spine. The latter failed to note, however, that in characteristic cases of one type the involvement of the costovertebral articulations was of a degree never seen in "Spondylitis Deformans." Glaser²⁴ laid particular emphasis on the occurrence of the disease in young adults of the male sex. Pribram⁶⁷ stated that "generalized ankylosis of the vertebral column" had a definite pathology as described by Marie. As for Bechterew's cases he believed that the lesions were essentially local. Reuter⁵⁹ and Siven⁷² were of the same opinion. The latter reported 4 cases in which roentgenographic studies had been made.

In 1904 two papers on this subject appeared in the same issue of the same journal. The first by Simmonds,⁷¹ presented a particularly lucid description of the pathologic anatomy of spondylarthrosis ankylopoietica and spondylitis deformans. Simmonds stated that he believed spondylitis deformans was a condition that appeared secondary to damage of the intervertebral disks. In his 2 cases of "ankylosing spondylitis" all of the intervertebral and costovertebral articulations were ankylosed. The intervertebral disks appeared somewhat thinned but were completely intact. The surfaces about the joints were smooth excepting for an isolated exostosis present on one lumbar vertebra. The posterior articular processes were ankylosed without exostosis formation. There was extensive ossification of the ligaments including the ligamenta flava. The other article, by Fraenkel,^{19a} confirmed the findings of Simmonds. Fraenkel emphasized that bony ankylosis of the costovertebral joints was rare in "Spondylitis Deformans," and never generalized. He drew the material for his discussion of "ankylosing arthritis of the vertebral column" from 4 cases which had come to autopsy. Like Simmonds, he stressed the constant finding of bony union between the posterior articular processes, and emphasized the fact that the vertebral bodies and intervertebral disks were intact. Neither he nor Simmonds was able to distinguish between a Bechterew and a Strümpell-Marie type. With these two papers the anatomic changes in the spine in spondylarthrosis ankylopoietica were stated in unmistakable terms. The cases reported by these authors had been followed clinically and studied at the autopsy table. No longer could the objection be raised that findings on isolated skeletons without clinical histories were being ascribed to these cases.

In 1906 Schlayer⁶⁴ presented the first good discussion of the roentgenographic findings. He demonstrated, for the first time on a roentgenogram, ankylosis of the posterior vertebral articulations. This he was able to do in 11 out of 12 cases. He was thus able to confirm the findings of Fraenkel and Simmonds. Furthermore, he was able to explain the confusion that had attended attempts to classify cases as Bechterew or Strümpell-Marie. He showed conclusively that the cases which were clinically Strümpell-Marie were true "ankylosing spondylo-arthritis," while cases that were clinically Bechterew might either be "ankylosing spondylo-arthritis" or "Spondylitis Deformans" with dorsal kyphosis. In 1907 Fraenkel^{19b} reviewed the subject, adding reports on specimens from 2 more cases and using the name "Spondylarthrosis Ankylopoietica."

We believe with Max Lange⁴² that it is less confusing if we forget the names of Bechterew, Pierre Marie and Strümpell when considering cases of

rigid spine, and think in terms of spondylarthrosis as opposed to other diseases of the spine such as infectious spondylitis and hypertrophic osteoarthrosis (spondylitis deformans and hypertrophic arthritis). Certainly the evidence points to the fact that Bechterew was not describing a pathological entity.

Pathology. In recent years important features of the pathologic anatomy of spondylarthrosis ankylopoietica have been added to our knowledge of the disease, notably the changes which occur in and



FIG. 1.—Lumbosacral spine and pelvis in Case O.R. showing marked bone atrophy, complete fusion of the posterior intervertebral articulations, incomplete calcification of the longitudinal ligaments, intact intervertebral disks, complete fusion of the sacro-iliac joints, exostoses on the ischia, and changes in and about the hip joints.

about the pelvic girdle. Nothing, however, has been added to the observations of Simmonds and Fraenkel on the gross changes as they affect the spine itself.

Although these and other authors had referred to involvement of the sacro-iliac joints, Krebs and Vontz^{38,39} (1934) seem to have been the first to recognize that this constitutes an essential part of the disease. Krebs³⁸ believes that the finding of changes in the sacro-iliac joint is the earliest and most characteristic sign. This view is

consistent with our finding of well-developed changes in the sacro-iliac joints at a time when involvement of the posterior vertebral articulations was slight (Cases K. J., R. G., and W. K.). In all of Wolff's 15 cases there was a more or less pronounced calcification of the sacro-iliac joints. The first demonstrable abnormality, according to Vontz,⁸⁴ is a spotty loss of contour of the joint surfaces and narrowing of the joint space.

Krebs and Vontz described the occurrence of patchy areas of increased density in the ischia and pubes with roughening of the periosteum and exostosis formation. Krebs interpreted this as evidence for a diseased state of the periosteum and adjacent fibrous tissue. He also described "ulcerous" defects at the symphysis pubis and bridging of the symphysis. Such changes were a prominent feature in many of our cases, and in one (R. Q.) they were observed fairly early in the course of the disease.

In the spine itself involvement of the small posterior intervertebral articulations is of primary interest. Guntz²⁸ was able to study histologic preparations representing various stages of this process. In the early stage there is inflammation of the joint surfaces with exudation, invasion of the cartilage by round cells, and production of connective tissue. With further progress of the disease only islands of cartilage remain, and finally complete bony ankylosis takes place. This process, although it does not involve all of these joints simultaneously, is never an isolated affair limited to one or two joints. The same is true of the destruction and eventual ankylosis of the costovertebral articulations. Exostosis formation about these joints is rare.

The essential change in the bodies of the vertebræ is a high-grade atrophy which appears early in the course of the disease (Schmorl⁶⁶). There is no tendency for the vertebræ to collapse. The intervertebral disks are remarkably immune from active involvement throughout most of the course of the disease, and the intervertebral spaces remain intact in the presence of a generalized involvement of all of the other vertebral articular surfaces. In preparations from individuals who had had the disease for many years, however, Schmorl found some tendency to narrowing of the intervertebral spaces and observed the presence of spongy bone in the intervertebral disks.

Fraenkel and many others believe that calcification of the longitudinal ligaments of the spine occurs secondarily to ankylosis of the small intervertebral articulations. Schmorl⁶⁶ is not so certain that this is the case, and Ehrlich^{15a} has reported cases where there was a marked "bamboo spine" without demonstrable involvement of the small joints. Oppenheimer,⁵⁵ however, states that ossification of the ligamenta flava occurs about the time that ankylosis of the small joints becomes bony, and that ossification of all of the longitudinal ligaments never occurs until ankylosis of the small joints in the affected region is complete. In our series of cases there is no

instance in which there was Roentgen ray evidence of calcification of the longitudinal ligaments in the absence of demonstrable involvement of the small articulations. In several instances (K. J., R. Q., R. W., J. C., and W. J.) the reverse was observed. Vontz⁸⁴ believes that ossification of the longitudinal ligaments begins in the region of the twelfth dorsal vertebra.

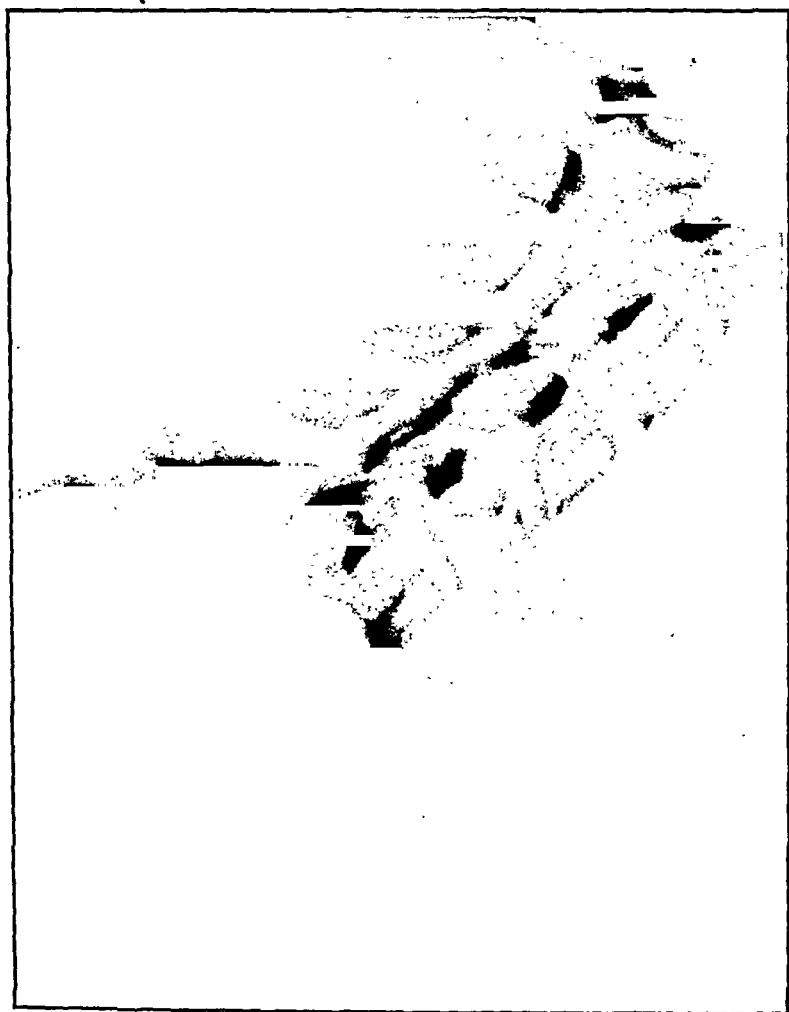


FIG. 2.—Lateral view of cervical spine in Case O.R. showing incomplete calcification of the anterior longitudinal ligaments.

Roentgenograms of the spine made in the anterior posterior diameter often show three longitudinal streaks of increased density. The middle one is believed by Ehrlich¹⁵⁸ to represent calcification of the ligamentum apicum. Careful study of preserved specimens has convinced him that the two lateral streaks are produced by an increased density of the joint processes of the posterior articulations

and of the joints themselves. We feel that calcification of the anterior ligaments, the ligamenta flava, the capsular, the supraspinous and the interspinous ligaments is the result of a reparative process secondary to the loss of normal articular support of the spine. The decalcification and partial absorption of the previously noted ligamentous ossification in the region of operative fusion is consistent with this view.

In our experience, in cases with associated involvement of the hip and shoulder joints, the disease in these joints resembles a severe atrophic arthritis. In a few instances there was considerable exostosis formation and calcification about the hip joints. This may represent a process similar to that described above as occurring on the ischia and pubes. It is interesting in this connection that Valentini⁸³ in 1899 believed that the loss of motion in the hip joints was due, not to an ankylosis between the head of the femur and the acetabulum, but rather to ossification of the joint capsule. Occasionally the temporo-mandibular joints are included in the ankylosing process. Ankylosis of the sterno-clavicular joints and of the shoulder joints proper, although reported, is rare.

Clinical Picture. Spondylarthritis ankylopoietica appears characteristically in young adults of the male sex, during the third and fourth decades of life. The onset may have been preceded by an acute or chronic infection of almost any sort, by one or more attacks of "acute polyarthritis," or by acute or chronic trauma to the spine. The onset may be acute but is usually insidious. In a few instances vague abdominal pains in the epigastric region and pains in and about peripheral joints occur. Although progressive stiffening of the spine may proceed for long periods of time without pain, this sooner or later makes its appearance, usually at first in the region of the sacrum and lower spine, but occasionally in the cervical region. The pain is subject to frequent fluctuations in intensity. As an early manifestation many patients complain of gradually increasing limitation of motion of the hips and lower extremities. Krebs³⁹ has pointed out that because of the lack of any very definite objective findings in the earliest stages of the disease, individuals suffering from it are often mistaken for malingerers and neurotics.

Examination of a patient in whom the disease is well established reveals the fact that the entire lumbar and dorsal spine is rigid. There is absence of the normal lumbar lordosis, and there may even be forward bowing in this region resulting in prominent creases across the abdomen. The upper part of the trunk is thrust forward. Abdominal type of respiration and decreased expansion of the chest are frequently quite noticeable. When the cervical region has become involved the head may be bent forward and held almost rigid on the neck. Kyphosis, when present, occurs in the cervical and upper thoracic regions. All grades of disability are encountered, depending on the duration and severity of the disease and whether

or not there is concomitant involvement of the hip and shoulder joints. Emaciation and loss of muscle tone is often very striking but is by no means an essential part of the picture. The latter finding has been given almost diagnostic significance by Grabowski.²⁷ In advanced cases we observed hypersensitivity, rigidity and spasm of the dorsal muscles and quite often muscle atrophy in the dorso-lumbar region. Signs of root irritation are not uncommon.



FIG. 3.—Lumbosacral spine in an early case of osteoarthritis of the spine showing spur formation and intact sacro-iliac joints.

Other findings which should be mentioned are the by no means constant presence of low-grade fever, the equally inconstant presence of leukocytosis, and the not infrequent occurrence of anemia. The sedimentation rate, however, is almost invariably elevated far above normal during the active stages of the disease. Whether this statement holds true for very early stages of the disease is not known. The most important and frequent complications, in our experience, are pulmonary tuberculosis, iritis, pericarditis, and pneumonia.

Diagnosis. The diagnosis of spondylarthrosis ankylopoietica may easily be suspected on physical examination alone. Vontz⁸⁴ maintains that a diagnosis in the early stages of the disease can and must be made on clinical grounds, because several months or even years may elapse before characteristic changes can be demonstrated by roentgenography. Koch³⁵ was able to study the early changes in the spine in one case. The first roentgenographic examination made one year after the onset of symptoms showed only a spotty atrophy about the posterior articulations in the lumbar region. Two years later, beginning ankylosis of these joints was demonstrated. Demonstration of changes in the sacro-iliac joints makes the diagnosis more certain. Lassen⁴³ asserts that these changes enable one to make a diagnosis very early. Unfortunately they are not specific and characteristic for this disease only. When involvement of the posterior intervertebral articulations is clearly demonstrated the diagnosis is established.

ROENTGENOGRAPHIC DIAGNOSIS. The usual Roentgen examination in sagittal and frontal diameters of the entire spine, plus special examinations of suspected areas in both obliques will demonstrate the anatomic lesions of the small joints and surrounding structures. It is important to bear in mind that the lesions may be well developed in one region while in others there may be only minimal involvement. The Roentgen findings according to the different stages consist in decalcification about the joints, blurring of the joint surfaces, narrowing and obliteration of the joint spaces, and areas of continuous calcification along the outer aspects of the vertebræ. Aside from those instances in older patients where there co-exists an hypertrophic arthritis, the vertebral bodies and intervertebral disks are well preserved and normal in contour.

DIFFERENTIAL DIAGNOSIS. The differential diagnosis of spondylarthrosis ankylopoietica is principally concerned with hypertrophic arthritis of the spine. In the latter condition the onset of symptoms occurs, in 80% of cases, after the fourth decade of life (Krebs^{38a}). The sedimentation rate is not elevated, and fever and leukocytosis are uncommon. In hypertrophic arthritis of the spine there is a degeneration of the intervertebral disk with narrowing of the intervertebral spaces, formation of exostoses about the edges of the bodies of the vertebræ and more or less marked wedging of the vertebral bodies. In advanced cases true bony bridging occurs. These changes are strikingly absent in cases of spondylarthrosis ankylopoietica. There may also be present a coarse calcification localized to the anterior surface of the vertebral column, especially in the thoracic region. Changes about the costovertebral and posterior vertebral articulations are not commonly demonstrated in hypertrophic arthritis and when present consist in exostosis formation. Ankylosis of these joints does occur, but is never generalized. Ankylosis of the sacro-iliac joints, according to Saskin,⁶² is present in the

majority of males by the fifth decade of life, hence examination of this joint offers little in the differential diagnosis.

The occurrence of only a slight elevation of temperature in the presence of a marked elevation of the sedimentation rate should be helpful in distinguishing spondylarthrit^{is} ankylopoi^{et}ica from tuberculosis of the spine.

Brief mention should be made of other types of cases in which a painful rigid spine is the chief symptom. We have studied roentgenograms from 16 such cases, and in all instances there has been evidence of disease in the sacro-iliac joints. There were 2 cases in young adult males of true infectious spondylitis as described by Sternberg.⁷⁶ There was 1 case of rigid spine, also occurring in a young man, in which lesions could be demonstrated only in the sacro-iliac joints. There were 13 cases in young adult males in which the roentgenographic findings were limited to complete or partial fusion of the sacro-iliac joints with isolated but very prominent exostoses on the vertebræ. Recently Doub¹⁴ has described a syndrome in which there is a noticeable lack of changes in the lower spine. It consists in the presence of a rounded kyphosis of the dorsal spine with narrowing of the intervertebral disks, and varying degrees of bone production, sometimes leading to complete bony fusion of the vertebræ.

TREATMENT. General hygienic measures are of the utmost importance. They should include adequate physical and mental rest, good nursing care, a complete high-vitamin diet, ultra-violet irradiation (natural or artificial), correction of constipation when present, occupational therapy, and a congenial atmosphere. When feasible, patients should be spared the rigors of our northern winters. They will profit considerably from extended periods of residence in the warm even climate of the Caribbean or the dryer climate of our Southwest. In either case we feel that worthwhile results can be achieved only if the time spent in these regions is reckoned in months, or better in years, rather than in weeks, and if other forms of treatment are continued under careful medical supervision.

Salicylates contribute considerably to the comfort of the patient and are a time-honored remedy for rheumatic conditions. Pyramidon is even more effective but should be used with caution and only if the granulocyte count is constantly watched. The administration of calcium in the form of calcium gluconate is in our opinion desirable in the presence of the extreme bone atrophy met with in this disease, and in spite of the tendency to calcification of ligamentous structures. Gold salts have been recommended. Arsenic compounds, iodides, colloidal sulphur and other drugs have had their advocates.

Anemia if present should be corrected by iron or iron and liver therapy. Transfusions of whole blood will not only raise the blood hemoglobin, but also, in some instances, will result in an improvement in the patient's condition greater than can be attributed solely to the improvement in the blood picture.

Vaccines, whether autogenous or stock, are in our opinion uncertain in action and any favorable effect from their use is for the most part to be attributed to a non-specific action. Fever induced by foreign proteins such as typhoid vaccine or by mechanical devices may induce striking remissions, but this type of therapy should be used with the utmost caution, and only when the patient's general condition warrants it.

Infected foci should be treated and, where possible, removed. It should be borne in mind in this connection that untimely efforts in this direction may result in a severe exacerbation of the disease.

The intelligent use of physiotherapy is of the greatest importance and should be conducted along conservative lines. Local heat administered by long and short wave equipment supplemented by gentle massage contributes greatly to the patient's sense of well-being, prevents muscle atrophy and contractures, and promotes restoration of normal muscle tone and function if the latter is already impaired. Carefully supervised active and passive exercises with or without balneotherapy are helpful in achieving the same ends. Thomsen⁸⁰ has advised the use of a tight abdominal binder to increase thoracic respiration. Deep breathing exercises are recommended by Tyson⁸² who also advises his patients to learn to sleep on their backs.

Orthopedic procedures should be directed primarily to relieving strain on the inflamed structures and to the prevention and correction of deformities. Swaim⁷⁸ found that the latter could be achieved by the use of plaster jackets, while good position once attained could be maintained by leather jackets.

PROGNOSIS. Although spondylarthrosis ankylopoietica may cease to progress at almost any stage in its development, it is usually slowly progressive, subject to remission and exacerbation, and gives the patient little peace until at the end of 10 or 20 years bony ankylosis is established, and there is cessation of pain. The amount of permanent crippling will depend upon the timely institution of orthopedic measures in an effort to minimize deformity and prevent ankylosis of the hip or other peripheral joints when they are involved. Ködderman³⁶ has drawn attention to the occurrence of "*formes frustes*," in which there are few symptoms and in which the therapeutic results are excellent. Rumpel⁶⁰ has pointed out that the presence of a rigid thorax favors intercurrent pulmonary infection as a cause of death in patients with spondylarthrosis ankylopoietica.

Discussion. *Incidence:* Schmorl⁶⁶ found 8 cases of spondylarthrosis ankylopoietica among the 10,000 specimens of vertebral columns in the Dresden Collection, an incidence of less than 0.1%. In Bachman's⁴ series of 2561 Roentgen ray films of the spine there were 41 clear-cut cases. Among 640 films which Haenisch made available for study by Bachman there were 6 cases of the disease.

Taken together Bachman's figures indicate an incidence of 1.5% in a large series of Roentgen ray films of the spine taken for various reasons. Krebs,^{38a} among 202 cases of stiffness of the spine, found 21 cases of spondylarthrosis ankylopoietica; the rest he classified as "spondylose deformans." It is obvious from the above that this disease is not rare, but that its true incidence must be less than 0.1%.

Seventeen of our 20 patients experienced their first symptoms prior to the thirtieth year of life. The earliest age of onset was 18, and the latest 40. In Fischer's¹⁷ series of 100 cases, 44 began in the third decade of life, 32 in the fourth decade, 13 in the fifth decade and 6 in the sixth decade. Three cases date from the second decade. In Krebs's^{38a} series of 21 cases, 62% began in the third and fourth decades of life, while in his series of 181 cases of "spondylosis deformans" only 20% experienced their first symptoms in those decades.

There is a striking unanimity of opinion as to the sex incidence of spondylarthrosis ankylopoietica.^{17,20,25,38a,58} In our series of patients there were no females. All of Fischer's¹⁷ 100 cases were in males. Buckley's⁹ series contains the highest incidence of cases in women. Six out of 60 (10%) of his cases occurred in females. He was unable to discover definite endocrine disturbances among these.

Since the diagnosis of spondylarthrosis ankylopoietica has been placed on a fairly firm basis, there has not appeared, to our knowledge, any good evidence that the disease is familial, although occasionally two members of the same family may have the disease. Many authors, especially those who believe that the disease represents atrophic arthritis as it affects the spine maintain that hereditary constitutional factors are of great importance. The sex and age distribution of this disease indicates that fundamental constitutional factors, whether they be of an endocrine nature or not, are important in determining susceptibility to it.

Since the first paper of Fraenkel,^{19a} trauma has been discussed as a possible etiologic factor in spondylarthrosis ankylopoietica. Krebs and Vontz³⁹ have called attention to the fact that the disease may develop asymptotically until an incident of trauma has occurred. Wehrsig⁸⁵ maintains that trauma, acute or chronic, is a factor in 25% of cases. By and large, trauma has not been a prominent feature in our records.

Proebster⁵⁸ believes that acute or chronic chilling is important in the etiology of spondylarthrosis ankylopoietica and calls attention to the fact that many patients date the onset of their disease from war service. One of the patients in our series (E. G.) was quite certain that this was true in his case. Wolff,⁸⁷ however, is skeptical of these stories. He investigated a number of such cases and found that in almost every instance the patient had had either episodes of pain in the spine prior to his World War service or one or more attacks of acute peripheral arthritis.

Evidence for the Infectious Nature of Spondylarthritis Ankylopoietica.—The etiology of spondylarthritis is as obscure as that of atrophic arthritis. They are both, presumably, infectious diseases. In both the sedimentation rate is elevated during the active stages. There is usually a low-grade fever and frequently a slight elevation of the white blood count. These last are not marked unless there is an active infectious complication such as pneumonia, pericarditis or pulmonary tuberculosis. The sedimentation rate, however, may be extremely high in both diseases even when no active local infection can be discovered. In both conditions the paranasal sinuses and teeth are often found to be in an unhealthy state, but whether they should be considered as harboring primary and etiologically significant foci of infection, or whether their tendency to become infected is merely evidence of the generally debilitated state of the patient cannot be definitely asserted. The lesion in the posterior intervertebral joints is certainly that of an infectious process. Lux,⁴⁶ who believes that focal infection causes spondylarthritis ankylopoietica, has called attention to the severe exacerbations which accompany intercurrent infections. The same, however, occurs in diabetes and pernicious anemia. Wolff⁸⁸ stresses the point mentioned above, and as further argument cites the frequency of eye complications and anemia, as well as the therapeutic response to removal of infected foci, the administration of pyramidon, and treatment with gold salts. Five of our cases developed after acute infections.

Originally Marie⁴⁸ felt that gonorrhea had nothing to do with the disease, but he later⁵⁰ revised this opinion and stated that gonorrhea could cause typical spondylose rhizomélisque. Sol⁷³ believes that the spinal involvement seen in cases of chronic gonorrhea is characteristic of spondylarthritis ankylopoietica. Wolff⁸⁷ and Bottoli⁶ believe that chronic gonorrhea is of etiologic significance. Although several of his patients had had gonorrhea, Touw⁸¹ does not believe that there is any relationship between the two conditions. In our series of cases, one (J. C.) definitely followed acute gonorrhea, another (O. R.) was associated with a second attack of gonorrhea or reactivation of an old infection. We believe that gonorrhea may be causally related to spondylarthritis ankylopoietica, but probably not in a specific sense.

There were present consistently, in the urine of 14 of our patients, occasional to 10 to 15 white blood cells per high power field. This fact indicates that a low-grade urinary tract infection, gonorrheal or otherwise, is frequently present in this disease. Forestier¹⁸ believes that the primary focus is in the genito-urinary system, and that toxic products are drained to the pelvis and spine by way of the lymphatics. Kienböck³³ relates the disease to tuberculous infection of the genito-urinary system. No pathologic evidence has yet been presented to substantiate either theory.

Although most authors have inclined towards the view that we are

dealing with an infectious disease other theories have been advanced. Steffens⁷⁵ believes that spondylarthrosis ankylopoietica results from a fundamental endogenous metabolic or endocrine disturbance. A few years ago there was a flurry of interest in a possible relationship between parathyroid dyscrasia and spondylarthrosis. Ssamarin⁷⁴ reported a group of 55 patients on whom he did parathyroidectomies. The pre-operative serum calcium values were remarkably high. Leriche and Jung⁴⁴ reported parathyroidectomies done on 3 patients with abnormally high serum calcium values. Funsten²¹ treated various types of "spondylitis" by parathyroidectomy and felt that the results were satisfactory. Compere¹¹ was unable to discover any evidence of dysfunction of the parathyroid glands in cases of spondylarthrosis ankylopoietica. The authors agree with Welti⁸⁶ that the figures given by Ssamarin are open to question, and that at present there is no convincing evidence that the parathyroid gland plays a rôle in the ordinary case of spondylarthrosis ankylopoietica.

Pulmonary tuberculosis is a serious complication of spondylarthrosis ankylopoietica. One of the patients whose case was reported in Fraenkel's first paper^{19a} died from this disease. According to Proebster,⁵⁸ Poncet, in 1903, reported 3 cases of "spondylose rhizomélisque" which he believed were the result of tuberculosis. Fischer and Vontz¹⁷ found active pulmonary tuberculosis in 3 of their 100 cases. Like Krebs^{38a} they found a lower incidence of this complication than anticipated. The high incidence of pulmonary tuberculosis in our series of cases (25%) is partly to be attributed to the fact that the Desert Sanatorium attracts a considerable number of tuberculous patients. Among the 201 cases of atrophic arthritis, however, the incidence of active pulmonary tuberculosis was only 2½%. In none of the patients with spondylarthrosis ankylopoietica and active pulmonary tuberculosis was the tuberculosis diagnosed until at least 1 year after the onset of symptoms in the spine. Two of these patients eventually died of the pulmonary disease. No patients with spondylarthrosis developed active pulmonary tuberculosis while at the Sanatorium. Two patients in our series showed Roentgen ray evidences of healed apical tuberculosis.

Recently Scott⁶⁹ has postulated that spondylarthrosis ankylopoietica is the result of active infection, usually tuberculous, of the sacro-iliac joints. Kienböck³³ has stated that the disease is an exudative synostosing form of joint tuberculosis, the infection proceeding to the spine by way of the lymphatics from a latent tuberculosis of the genito-urinary tract. Neither author offers any substantial evidence to support his view. Fischer and Vontz¹⁷ tested patients with subcutaneous inoculations of tuberculin. The reaction was never focal and rarely general. Assman³ concluded with Fraenkel that the pulmonary disease is not causally related to the disease in the spine, and is either secondary to it or merely incidental. The authors of the present paper are in accord with this view.

The incidence of iritis in patients with spondylarthrosis ankylopoietica is not very well known. Fischer and Vontz¹⁷ observed its presence in 3 of their series of 100 cases. Wolff⁸⁷ found it had been present in 6 of 15 cases. In Golding's²⁵ series of 124 cases, it had been present in 5.6% of the cases. It was present at some time during the course of the spondylarthrosis in 5 of our cases, that is, in 25%. In the 201 cases of atrophic arthritis, the incidence of iritis was 2%, while among the 95 cases of hypertrophic arthritis there were no cases of iritis. Sol⁷³ feels that iritis is particularly characteristic of the spondylitis which results from a chronic gonorrheal infection. In none of our cases with iritis was there any evidence of gonorrheal infection. It is of interest and perhaps suggestive of a "rheumatic" basis for the iritis that in 1 of these patients (R. Q.) there was definite evidence of disease of the mitral valve, and that 2 other patients (E. H. and W. B.) each had a pericarditis at the time of at least one of their attacks of iritis. Teschendorf⁷⁹ and Kraupa³⁷ believe the iritis is merely a sign of a general infection. The former took roentgenograms of the spine in a series of cases of iritis and discovered 6 cases of frank spondylarthrosis ankylopoietica, and 3 instances, in patients who were entirely symptom free, where changes were present in the spine characteristic of the disease. Ascher² calls attention to the grave prognosis in the iritis which occurs with spondylarthrosis. Kunz,⁴¹ found evidence of tuberculous infection in only 1 of 7 cases with iritis. None of the cases in our series with active or inactive tuberculosis had iritis. That iritis is an important complication of spondylarthrosis ankylopoietica is certain, but its relationship to the process in the spine has yet to be defined.

Spondylarthrosis ankylopoietica can develop in patients with a typical atrophic arthritis (Proebster). Chalmers¹⁰ believes that "spondylarthrosis atrophica" is a manifestation of rheumatoid arthritis. Fischer¹⁷ found evidence in his study that suggested a possible relationship between acute rheumatic fever and spondylarthrosis ankylopoietica. In 11 of his 100 cases there was frank valvular disease of the heart. In 4 of these cases there had been an acute polyarthritis prior to the onset of the spondylarthrosis; in 2, there had been a gradual swelling of certain peripheral joints simultaneously with the development of the spinal disease. Krebs and Vontz³⁹ cite a case which followed acute rheumatic fever with involvement of the aortic valve.

Two of our patients (R. Q. and R. C.) had had rheumatic fever some years prior to the onset of the spondylarthrosis. One of them (R. Q.) had a definite lesion of the mitral valve. In 3 cases there was clinical evidence of atrophic arthritis of the small joints of the extremities (J. C., W. K., and H. M.).

Whether spondylarthrosis ankylopoietica should be classified as a disease sui generis or be considered as the spinal form of atrophic arthritis is difficult to decide. The fact that the majority of patients suffer from active disease of the spine for many years without

involvement of the small joints of the extremities seems to indicate that the two conditions are not the same. In our opinion spondylarthrosis ankylopoietica belongs to the group of so-called rheumatic and rheumatic-infectious diseases. Its striking predilection for members of the male sex sets this lesion in a class apart, at least until the etiology of this and the other rheumatic diseases is clarified.

Summary. 1. We have reviewed the development of the concept of spondylarthrosis ankylopoietica as a disease distinct from "spondylitis deformans."

2. A statistical study of 20 cases of this disease has been presented as a basis for discussion.

3. The pathologic anatomy of spondylarthrosis ankylopoietica has been described with particular reference to the changes in and about the pelvic girdle.

4. The clinical picture and the problems of diagnosis and treatment have been presented.

5. The significance of iritis and tuberculosis as complicating conditions has been discussed.

6. We have reaffirmed the infectious nature of spondylarthrosis ankylopoietica, at the same time emphasizing the fact that constitutional factors are fundamental as shown by the age and sex distribution of this disease.

7. The relationship of spondylarthrosis ankylopoietica to the problem of rheumatism has been discussed.

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NUTRITIONAL ASPECTS OF THE TREATMENT OF ARTHRITIS.

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In a presidential address before the American Rheumatism Association,^{16b} one of the present authors endeavored to reduce to a brief compass a few principles and broad considerations illustrative of

the clinical philosophy which he holds toward the field of arthritic diseases in general. The generic nature of the problem was emphasized and also the therapeutic corollary that treatment of the arthritic should proceed along many lines. The response to this effort has suggested that a further exposition of some of the considerations there advanced might be of value to those who treat arthritics.

There is still much contemplation of disease as a process involving one organ, one system or one mechanism alone, whereas many chronic disease states present an interwoven pattern of disturbances in several parts of the body, no single one of which disturbances is always dominant. This is especially true of arthritis. The number and variety of therapeutic considerations to be thus entertained toward the problem of arthritis is, indeed, so considerable that, in most attempts at exposition of them, only titular references can be made because of limitations of space. Furthermore, there is a general, and perhaps natural, assumption of familiarity with details of therapy falling under significant but apparently obvious captions such as local rest, systemic rest, betterment of circulation and optimal nutrition, which is not always justified, so far as effective application to the treatment of arthritics is concerned. For these reasons, we are persuaded that recommendations of therapy made along generic lines often fall short of their purpose and that the need of emphasis upon detail is greater than might be supposed. We also believe that therapy should be more pointedly directional than is usually the case.

The syndrome of the chronic arthritides is now universally recognized as consisting of at least two great types, namely, atrophic or rheumatoid arthritis, and hypertrophic or osteo-arthritis. Chronic arthritis at large, however, was well defined by the American Committee for the Control of Rheumatism¹ as a systemic disease with joint manifestations and in many cases of the true syndrome, especially in the atrophic group, the joint disturbances are minimal, the disability being chiefly in the tendons, fibrous tissues, muscular tissues, nervous system or elsewhere. Such instances emphasize the fact that the syndrome concerns primarily the mesodermal tissues as a whole and that the term "arthritis" is either a misnomer or inadequate. The term "rheumatism" covers the field rather better, although somewhat vaguely, and it is possible that we may later come to some such definition as "mesodermosis," which would carry a desired implication of wide distribution because of chief involvement of the derivatives of one of the blastodermic layers of the embryo. The use of this term here is only illustrative, but the point of view suggested by such nomenclature emphasizes the fact that many factors influence the several expressions of the syndrome.

The full nature of the problems presented by arthritis has not

yet been revealed with finality and all of the links in the chain between suspected etiologic factors and the developed disease have not been forged. We are satisfied, however, that enough is known to justify the statement that the syndrome of arthritis is susceptible of fuller control, both preventive and arresting, than is yet exercised toward it, except in a few selected centers of study. Even in some such highly regarded centers the emphasis has often been on a few single factors of etiology or therapy, to the incidental or intentional exclusion of a host of considerations which may be equally significant in the care of the patient. Gregg⁸ recently remarked "Some of the finest teaching can take place when there is much to discover and but little as yet to indoctrinate," and to few medical fields is this thought more relevant, perhaps, than to that of rheumatoid disease. In a syndrome of uncertain origin so varied as is arthritis it is next to futile to expect instant clarification by a laboratory or clinical "tour de force." Certainly none has been forthcoming to date. It follows, therefore, that there is both propriety and necessity in scrutinizing each component of therapy in relation to the whole and in weaving them together.

There has been needless controversy as to which factors of therapy should be stressed. The fact is that all well-considered factors should form part of a coördinated approach and should be played upon as a keyboard rather than separately as in the sounding of a single note. For these reasons the present contribution will enter into greater detail regarding some of the therapeutic recommendations referred to above. As it is obviously impossible to cover the therapy of arthritis within the compass of a brief article, attention will therefore be confined chiefly to one phase of therapy which, in particular, often seems to be imperfectly grasped, namely, the application of nutritive principles to the physiologic needs of the arthritic. This will be discussed, however, not as a separate topic but in connection with that balanced outlook which envisages all of the deviations from normal presented by the arthritic as integral parts of the clinical problem. It is especially relevant at present to draw attention to nutritional and metabolic considerations since the reaction, now well under way among the profession, against that domination which the doctrine of focal infection long held over this field, justifies and indeed necessitates consideration of other factors suspected or known to have influence. The view is indeed developing in some quarters that the phenomena of arthritis may conceivably reflect, through such factors as infection, exposure, nervous strain, or faulty nutrition, a disturbance of equilibrium of the central nervous system and especially of the hormonal balance of the "master tissues." The peripheral expressions of such imbalance within the mesodermal tissues might be expected to be more or less symmetrical, as they often are in arthritis. With such an outlook, nutritive factors would obviously be only one of many groups of

factors involved, but they deserve consideration because of relationships and influences known to exist and to be open to modification. It is not too much to expect that some clinicians, inclined hitherto to overlook or minimize these factors, will now weigh them more carefully.

The broad bases of nutrition underlie several clear-cut and many less-defined clinical syndromes but appreciation of these relationships is far from widespread. Even the term "nutrition" still carries to many the implication, in the field of arthritis, of gross departures from average weights; namely, over-nutrition or under-nutrition; that is to say, adiposity or emaciation. Because of this limited concept, almost the only concern exercised is that the emaciated arthritic be fattened and the obese arthritic reduced. On broad grounds this principle is usually justified, so far as it goes, but between these extremes there is a wide sphere of influence to which scant attention is given. Furthermore, even the principle of fattening the thin and thinning the fat may not be prescribed indiscriminately, and in some instances in which imbalance of nutrition exists in less obvious degree, definite harm may be done to the arthritic subject, usually suffering already from many handicaps.

Nutrition shares with heredity the function of determining the constitution or general capacity of the body for maintenance of itself. Experimental animals bred from standardized stock may be made to develop into physically superior animals by providing optimal rations, or into dwarfed creatures with shortened life spans by reducing certain components of the diet to suboptimal levels. The development of deficiencies in progeny or individuals may be significantly influenced, even precipitated, by coincident infections and by altered physiologic mechanisms. Chronic nutritional deficiencies may permit pathogenic agents, such as bacteria, to become immediate factors in a given disease process. The reciprocal relationship of infectious factors and dietary adequacy appears to have an important bearing upon the arthritic. The growth of bacteria in tissues not only diverts certain materials required for such growth from their normal function in the maintenance of tissue, but also discharges into the circulation "toxic" products which combine for defensive purposes with still other substances, such as amino acids, to form inert products. These conjugated products are then eliminated from the body with a consequent net loss of various materials to the economy as a whole.

In this light, arthritis can be visualized as a disease of extraction, by virtue of the demands made by the metabolism of bacteria upon vitamins and tissue ingredients, as much as, or more than, one of invasion by bacteria as has so long been generally held. Dietary inadequacies may, further, lead to apparently minor gastro-intestinal disturbances which, only after years, eventually reflect the picture of a deficiency syndrome. Castle² has shown that an

asymptomatic abnormality of gastric secretion may induce a state of dietary deficiency in spite of the "adequacy" of the diet.

Not only deficiencies but also relative excesses of certain dietary factors lead to pathologic states. Attention may be called to the production of nephrosis by cystine or diets low in vitamin B;⁴ the exaggeration of nephritis by diets high in nucleoprotein,¹⁴ in contrast to simple protein; the production of beri-beri by excessive carbohydrate on a suboptimal intake of vitamin B₁;⁵ the production of cataract by diets high in galactose;¹³ the development of rickets by a high caloric intake on a basal diet otherwise adequate or low in vitamin D.¹²

Funk⁶ and McCarrison,¹¹ as well as Cowgill,³ have concluded that there is apparently a balance between the need for and the utilization of vitamins on the one hand and, on the other, the amounts of the other constituents of the dietary, such as protein and carbohydrate. These considerations imply, not that carbohydrate, for example, is "toxic," but rather that the body requires a minimal quota of thiamin and riboflavin for the enzymes essential to the metabolism of glucose. If the amounts of glucose exceed an optimal level the quota of vitamins is drawn upon, leaving lesser amounts to meet endogenous requirements.

There is no complete parallelism of arthritis with any known specific deficiency disease. Many cases present graphic evidence, however, of disturbed metabolism of a kind which could be accounted for upon such a basis, in part at least. These evidences include bone and muscle atrophy, anemia, low plasma protein, infiltration of fibrous tissue, degeneration of cartilage, low basal metabolism, decreased saturation with vitamin C, reduced glucose tolerance, diminished range of variability of skin temperature and disordered immunity.

The view that hypertrophic arthritis represents largely degenerative processes, probably involving errors of metabolism referable or amenable to nutritional influences, appears easy of acceptance. That atrophic arthritis, hitherto usually regarded as referable to infectious factors only, may be comparably influenced by nutritional factors, has been apparently more difficult of acceptance. There is as much reason, however, for the view that imbalanced nutrition may, with other factors, pave the way for invasion of bacteria conducive to arthritis in the young, as there is for the view that it may with other factors pave the way for "degenerative" factors conducive to arthritis later in life.

Again, and more specifically, it is becoming abundantly clear that along with the so-called "true" arthritides, atrophic and hypertrophic arthritis, with which fibrositis is also usually grouped, we have to deal with affections of joint structures or interarticular structures, sometimes classified as "arthroses." To what extent it is justifiable to segregate these states and to what extent they merge with the true arthritides is not finally determined, but it is

certain that they are related to the arthritic syndrome. The particular relevance of this is that in some such arthroses, hypothyroidism is demonstrably present, and, indeed, a somewhat lowered metabolic rate is met with in about 30% of all arthritics as a group. In some cases part of the lowered basal rate may derive from closure of some of the capillary beds, particularly in muscle,¹⁶ but the benefits following thyroid medication are so clear-cut in other instances as to leave no room for doubt that the thyroid itself is actually involved at times. Acceptance of this premise requires that metabolic processes at large, both exogenous and endogenous, be weighed in the etiologic and therapeutic scale, and that everything which influences intermediary metabolism should have consideration. In this sense, not only the quality and the proportions of the foodstuffs but the amount could be expected to have a significant influence, and there is, indeed, evidence that in some cases of arthritis a difference of some 350 calories may, under perfectly balanced conditions, be influential.

Although, as remarked above, there is no final evidence justifying classification of arthritis as a disease of dietary deficiency, recent Roentgen ray studies of the gastro-intestinal tract in 400 arthritics by Spackman *et al.*¹⁹ reveal that part of the picture characterizing experimental deficiency states in animals in respect to the vitamin B complex is to be seen with striking uniformity, almost as a pattern, in arthritics as compared with normals. The elongated and dilated gut induced by McCarrison *et al.*¹¹ in monkeys is closely simulated in arthritics, and there is general agreement that this situation is referable to faulty nutrition and secondary imbalance of the autonomic nervous system. One of the therapeutic corollaries to this state of affairs is the institution of optimal nutrition.

Optimal nutrition is a relative or comparative term, however. It can relate only to the best nutrition for the given subject and it is necessary to define the standards on which optimal nutrition may be predicated. Optimal nutrition in the broad sense implies maintenance of tissue in a milieu wherein the highest level of function can be exercised. Inasmuch as the function of tissues varies with a number of factors, the only type of prescription which can be presented is one which directs consideration to the particular needs to be met. For example, dietary supplies optimal for a normal adult subject may be inadequate for the person whose capacity for absorption is limited by gastro-intestinal dysfunction. Similarly, a diet adequate for the requirements of an organism previously well supplied with essential dietary materials is inadequate for the organism which has been poorly supplied or whose requirements for specific substances have been increased by the presence of competing forms, *i. e.*, bacteria or parasites. It is equally true that there are needs for specific dietary materials and favorable relative proportions of them during periods of modified physiologic function, such as occur in disease, and it is generally recognized that there are

increased demands during periods of increased energy output. Age and size also introduce variables. It is thus apparent that the establishment of optimal nutrition is not a matter of providing food elements in a stereotyped manner, but that it requires critical consideration of the particular favorable balance to be achieved, as well as of the factors operative to prevent this balance.

There is another aspect of the problem, exemplifying the special dietary adjustments required for achieving optimal nutrition in the arthritic, which is frequently overlooked. This concerns the low-grade edema presented by many arthritics. The whole significance and mechanism of this condition is not fully understood. Part of the "edema" may be referable to low plasma proteins but not all of it. In any event, there is small doubt that some of the symptomatology of the disease, especially some of the pain and stiffness, is referable to this "tissue edema," as can be easily demonstrated in suitable subjects.¹⁸ Thus arthritics may experience surprising benefit immediately following major operations, as is now familiar to many observers. Among the several conspicuous features associated with such remissions is the necessarily sharp curtailment in the caloric value of the dietary intake.

A diet which supplies less than the caloric requirement, if practised for a few days, may induce striking changes in the symptomatology of arthritis, particularly as regards swelling, pain, and limitation of motion. This is most likely to be found in patients under adequate conditions of rest and protection, and especially in those in whom infectious factors appear to be minimal or absent. This is a procedure fraught with great danger to the sick arthritic, however, and extreme application of it has sometimes brought discredit to such practice.

It should be noted that such practice, nevertheless, has become in many places a more or less routine measure of treatment. In one institution, treatment of arthritics is usually initiated by free catharsis accompanied by restriction of the diet to orange juice for 3 days. Routine practice of this sort is not justifiable and yet criticism can well attach to any attitude of the profession as a whole which ignores the nucleus of truth in such methods and forces patients to experience unwise applications of them. Some analogy to this is to be seen in that attitude on the part of orthodox medicine which ignored the benefits inherent in physical therapy, especially massage, and so drove countless persons to the receptive arms of osteopaths and other cultists.

von Noorden,¹⁵ Gerson⁷ and others have employed raw vegetable diets in the treatment of various diseases, including arthritis. The clinical improvement noted on this dietary regimen has been largely attributed to the fact that diets so constituted are low in sodium salts. Hare⁹ has recently employed a similar dietary regimen under controlled conditions in a series of 12 cases, as follows. Rations of uncooked foodstuffs consisting of approximately 145 gm.

of carbohydrates, 35 gm. protein and 143 gm. fat were supplied for a period of 2 weeks. Following this period, cooked foodstuffs of similar content were provided. In 8 of 12 instances marked improvement resulted in the soft tissue manifestations. Two cases experienced temporary benefit and the remaining 2 cases obtained no relief. The toxic symptoms and the bone lesions did not appear to be greatly modified. The favorable clinical result was associated with a rapid loss of tissue water during the first week of treatment. This response is attributed in large measure to a low sodium intake. Some emphasis was also placed upon the provision of adequate protein, fat and vitamins B and C.

The use of similarly modified diets which are relatively low in carbohydrates has led Pevsner *et al.*¹⁷ to the view that part of the clinical improvement upon such a regimen is to be attributed to a non-specific desensitization of the tissues to various undefined entities. Leporsky¹⁰ has noted clinical benefit following the use of diets which provide a limited supply of total calories. These observations are cited to illustrate the fact that, whereas different views are expressed as to the mechanism involved, there is rather widespread recognition of a significant therapeutic effect to be obtained by modified rations in arthritis.

Inspection of these various dietaries, however, reveals clearly that they are characterized by under-maintenance or mere-maintenance levels and that whatever other factors may be concerned, allegedly or otherwise, they all promote elimination of tissue fluids. This influence must of necessity bring about the consequences now to be referred to.

Turning, therefore, to the "edema" under discussion, it can be said with confidence that under appropriate conditions it can be favorably influenced or aggravated by varying the proportion of foodstuffs in the dietary which contribute to retention of water within the body. The foodstuff most influential in this connection is carbohydrate and for every gram of it stored there is also retained from 3 to 4 gm. of water. Storage of 1 gm. of fat leads to retention of only about 0.1 gm. of water, and protein leads to little or no retention of water, since it is rarely stored except after a debilitating state such as typhoid fever when a deficiency is to be made up. The catabolism of protein leads to the formation of materials which require water for excretion. Furthermore, in arthritis the plasma proteins may be low, especially albumin, so that part of the edema, though not all, may be referable to this basis, as remarked above. When this is the case, additional protein is necessary to correct the faulty colloid osmotic relationships. Whatever the full explanation of this low-grade edema of arthritis, importance attaches to all mechanisms influential in reducing it. Other measures contributory to this same end are purgation, sweating, possibly a low salt intake, certainly rest in recumbency, and massage. The first two mentioned form the basis of much of the therapy exhibited at the spas

of Europe and are not without danger. Massage is also a two-edged tool and must be used with care. None of these can be persisted in for extended periods. Furthermore, depletion of tissue water in these ways is largely negated unless continued restriction of fluid be observed. Control of tissue water by diet, if exercised intelligently, can be carried on more or less continuously and with less regard to the fluid intake. Indeed, on a mere-maintenance or sub-maintenance diet the food intake may be entirely liquid in form and yet the economy will lose water. The most immediate and graphic effects in reducing the above edema, with or without dietary influences, are probably to be seen in those atrophic arthritics who have been "carrying on" in spite of poor health and are then abruptly put to bed. Rest in recumbency promotes passage of fluid from tissues into vascular channels and may alone inaugurate changes within 3 days, often evidenced by a decrease in tissue tumefaction in the hands, revealing atrophied tissues and tendons previously hidden, as pointed out by Scull and Pemberton.¹⁸ If accompanied by a diet adequate in calories and protein, relatively high in fat and low in carbohydrate, this effect is intensified. The same dietary influence can often be observed in ambulant patients, though obviously handicapped then by adverse gravitational and physiologic factors.

It may fairly be said, therefore, that most arthritics will experience benefit upon a diet which provides an adequate supply of calories and is optimally balanced with respect to various components, along the lines discussed. Thirty calories per kilo afford a good starting point at rest except in those who are overweight, when this allowance is too high. In addition to other advantageous influences, rest in recumbency is of great importance in cutting down the caloric needs of the individual and permitting a lower intake *in toto*.

The diet should contain at least 1 gm. per kilo weight of protein of good biologic quality. This quantity has been found by the trial and error method to keep most patients in nitrogenous equilibrium. It is evident that the conspicuously underweight individual should be given more protein than this amount, whereas the grossly overweight patient may be given less. Emphasis should be placed upon the quality or source of the protein, since all proteins are not equivalent in the property of supporting growth, or presumably, in providing for the regeneration of wasted tissues. In further conformity with the general principles enunciated above, carbohydrate should supply from one-third to one-half of the remaining calories needed and fat should supply from one-half to two-thirds of the balance, unless intolerance for fat be manifested. In the average unrestricted dietaries of most persons these proportions are roughly reversed, especially in the lower wage groups. Along with the above there should be an abundance of inorganic salts and vitamins. Accessory feeding of the latter is usually indicated.

Some influence from the broad dietetic changes above discussed may perhaps be observed in most cases of arthritis but this influence can be of true therapeutic value only when "drugs" operating in an opposite direction have been removed or controlled. The more drastic measures of purgation and sweating, long advocated for arthritics, as well as salt restriction, are usually not necessary and should be reserved for sthenic cases.

It must be emphasized again that nutritive factors tending toward the reduction of tissue edema do not necessarily affect the basic cause or causes of arthritis. They may, in part, do this, but in any event they often definitely contribute toward betterment of a condition of the tissues which demonstrably aggravates the arthritis for purely physical reasons, and probably constitutes an important part of the true syndrome.

Enough has probably been said to illustrate the nutritive aspects of the therapy of arthritis and to explain why a casual approach to treatment as a whole, not to mention the nutritive aspects of it, so often fails of results. Medical literature contains many references to the "reserves" or "recuperative powers" of patients. These terms carry indefinite connotations, however, and there is practical, therapeutic advantage in all serious cases of arthritis in thinking more precisely in terms of the several actual dysequilibria in the major systems of the body which can frequently be shown to exist and to be open to amelioration. Among the dysequilibria thus encountered is that of faulty nutrition, using this term in a refined sense of the word. This constitutes a very frequent finding in arthritics. Even when no obvious or gross error is observable, modifications in the food intake along the lines and within the limits discussed may prove very beneficial. To apply these principles alone, however, without concern for other factors which are known to be operative basically, in many cases at least, such as infection, anemia, under-nutrition, reduced plasma proteins, gastro-intestinal dysfunction or nervous imbalance, may result not only in failure to obtain the desired improvement but possibly in further aggravation of the conditions present and in consequent discredit to physiologically sound procedures. Unless opportunity be given for dislocated processes of physiology to return toward normal by lessening the burdens on them from whatever cause, they remain dislocated. Removal of the original cause of this dislocation may no more correct the end results than repair of a faulty switch after derailment of a train restores the cars to the track. Minor factors, uninfluential alone, may suffice to perpetuate a dislocation originally brought about by very different agencies.

An easy or early demonstration of a reduction in tissue edema through the combined or separate influences of rest, sound dietetics, the sweat process, and so on, should not necessarily imply that any of these measures can be persisted in or applied routinely. Which

one, if any, should be stressed is entirely a matter of clinical judgment. Experience with the operation of these influences illuminates sharply the fact that a full perspective of the field is a requisite to adequate therapy. This perspective is not to be obtained through morphologic or *in vitro* studies alone; clinical developments can be equally informing. It is to this complex state of affairs that the problem of nutrition must be referred in the care of arthritics.

One of the confusing problems confronting the general practitioner is the apparent conflict among students of arthritis as to the alleged merits of therapeutic measures, on the one hand, and the paucity of proven etiologic factors, on the other. Thus, one group of students expresses the view that certain therapeutic measures are of great value, whereas another group counters that such measures should not be applied because there is no adequate evidence of their therapeutic relation to the disease. It is further stated by some that atrophic and hypertrophic arthritis are progressive diseases in that each disease runs its course regardless of the type of therapy instituted. The former disease is sometimes said to be arrested only when ankylosis is reached and the tissues are no longer reactive; whereas the latter, as manifested in Heberden's nodes, is arrested when calcification of tissue prevents further response.

While it has been repeatedly emphasized that arthritis is a systemic disease, the classification of the syndrome into two or more kinds of arthritis upon the basis of the articular lesions may erroneously limit attention to this aspect of the patient's difficulty. The patient, despite the fact that he may also suffer from anemia, nutritional imbalance and nervous manifestations, is actually told by some students of the subject that, because he has an atrophic lesion in his joints which cannot be undone, he has a hopeless condition, about which nothing of real importance is known and therefore nothing can be accomplished. Indeed, according to this negativistic school, a patient cannot be classified as an atrophic arthritic if his joints get better. By the same token, the patient with hypertrophic arthritis is advised, because he presents characteristic bony overgrowths, that he need not be concerned with focal infection in his teeth, since the removal of such infection has no proven relation to and therefore cannot cure the articular disorder.

It seems incredible that these points of view should have such wide acceptance among physicians whose declared purpose is to care for the whole of the patient who has rheumatic disease. This false philosophy arises from a well-intentioned attempt to be critical. A little learning, however, may be a dangerous thing. One should drink deeply or not at all at the Pierian Spring.

The practical deduction from these differences of opinion is that consideration of the syndrome of arthritis from one pathologic aspect or from an incomplete etiologic aspect alone, is inadequate for clinical purposes. This would make little difference, except academically, if it did not lead to undesirable limitations of treatment.

This definitely restrictive influence in arthritis results in a wrong application of the "all or none" law of physiology, that the response from a given stimulus must be maximal or it is without existence. The uncritical application of this notion is well seen in several ways. Thus the latest point of view toward focal infection is to the effect that since focal infection does not always produce proliferation of the synovial membrane it cannot have any immediate importance to the arthritic. Again, since systemic rest, from this point of view, does not alone arrest all cases of arthritis, it is alleged to be of no definitive value. Such an attitude constitutes loose thinking and cannot be condoned. Dispassionate reasoning dictates, for example, that attention should be given to the low metabolic rate found in a patient presenting rheumatoid disease, despite the fact that not all persons with rheumatoid disease present a low metabolic rate.

The chronic invalid is the subject of many disabilities, some of which are open to correction, others of which are inaccessible to any measures now available. Thus eroded cartilage cannot be replaced. Common sense again dictates, however, that those deviations which are open to correction, such as fatigue, edema, focal infection, should be regarded as integral parts of the problem and not dismissed as irrelevant because one feature of arthritis, say proliferation of the synovialis, is not specifically arrested thereby.

It is to be emphasized, however, that a patient may show marked improvement, amounting to full clinical relief, in the presence of an anemia which still persists and a sedimentation rate which remains elevated. This is not to be interpreted as evidence that anemia and an increased sedimentation are not to be regarded as important and constituting part of the picture. It is to be interpreted, however, as evidence that neither an increased sedimentation rate nor any other single factor, even articular lesions, can necessarily be regarded as a true criterion of the whole arthritic process. Incidentally, these considerations bring into relief the extent to which arthritic manifestations depend for their expression, in part at least, upon tissue edema. In some cases this condition may, indeed, seem almost to constitute the disease, so far as the patient's subjective and objective discomforts are concerned.

It has been well said that arthritis is a systemic disease with articular manifestations. It might be better, however, to say that patients ill with rheumatoid disease present a wide variety of symptoms which sometimes include articular disturbances. In this view the care of the patient with rheumatoid disease requires not the uniform application of a single measure to all, but rather the application to any patient of all measures which can in principle contribute to the correction of the various disturbances presented by arthritics as a group.

The field of arthritis still contains many therapeutic "defeatists" who, depending upon a few single agencies to correct the syndrome, experience frequent disappointment and come to believe that the

problem is intractable. Inquiry into such situations usually reveals that no real attempt has been made to pursue logically the physiologic leads available. William Penn once remarked, "Perhaps the worst part of this Vanity is its unteachableness. Tell it anything and it has known it long ago and outruns information and instruction." The arthritic patient is full of information for his medical adviser, but the adviser must have care lest he be "unteachable" and outrun instruction.

Conclusions. It is apparent that the widely held view is inadequate which regards the sole function of foodstuffs for the adult arthritic as limited to the provision of energy and regards all kinds of iso-caloric diets as equivalent for him. The proportion in which each dietary component is supplied is also important. In chronic and degenerative disease the proportions of the foodstuffs as well as the amounts should be given precise consideration.

Nutrition must thus be optimal not merely in respect to maintenance of a normal organism but also within the narrower necessities of the arthritic. The fact that arthritics may recover when the favorable influences of optimal nutrition, as above described, are not provided, in no way negates this truth. Arthritics may also recover in the presence of infections or without the benefits of physical therapy, but recovery may be significantly expedited if advantage be taken of all favorable influences which can be brought to bear by appropriate coördination of them. The various deviations from normal presented by arthritics as a group should be regarded as integral parts of the clinical problem. Certainly to deny to the struggling arthritic correction of these several deviations because the whole story is not understood and because no one of the factors involved alone induces or "cures" the disease, is to fail to see the problem in the light of all that modern medicine affords.

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THE WATERHOUSE-FRIDERICHSEN SYNDROME.

ACUTE BILATERAL SUPRARENAL HEMORRHAGE.

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No more dramatic episode may face the pediatrician than the evolution of the so-called Waterhouse-Friderichsen syndrome. Since Völcker¹⁸ first recorded a death within 24 hours of onset of illness in a 2-year-old infant, with necropsy findings of purpura and bilateral adrenal apoplexy, until this present report, a search of the literature has revealed but 89 cases. Since it is our opinion that this is a clinical entity too often neglected, we wish to reemphasize the salient features and record 7 cases of our own, in the confident expectation that others will be spurred to note their observations, and perhaps initiate appropriate treatment which might be life-saving.

Blaher and Bailey³ were apparently the first to record a group of cases which fitted the clinical picture which we recognize today; in 1901, they suggested that the etiology was a fulminating hemorrhagic smallpox and definitely inclined to the theory that it was "probably a blood poisoning of some form." In the same year, Graham Little¹¹ collected 11 similar cases and noted that the bacteriology was negative. In 1911, R. Waterhouse¹⁹ presented a case of his own and collected 15 from the literature; he claimed a distinctive clinical picture which had not heretofore been recognized, but added nothing as to the etiology. Then for the first time, in 1916, MacLagan and Cooke¹³ wrote of 2 cases of fulminating cerebrospinal fever with recovery of the meningococcus. When Friderichsen⁸ summarized the literature in 1918 the syndrome we now recognize assumed its title. Excellent contributions to the literature have since been made by various authors—Aegerter,¹ in 1936, Sacks,¹⁷ in 1937, and Kunstadter,¹⁰ in 1939, reviewed the published reports, the latter author collecting 74 cases. Since that publication approximately 14 cases have been added; the addition of our 7 cases brings the total to 96.

Symptoms. Ninety per cent of the cases occur in children varying from 6 months to 9 years; Aegerter¹ states that 70% of the patients have been under 2 years. In our series, the eldest was 6 years,

the youngest 6 months and the average 3.37 years; according to sex and race, there were 5 males and 2 females and 5 white and 2 colored infants. The typical anamnesis relates of a previously healthy child, who having gone peacefully to sleep, awakens with a cry. The signs and symptoms that follow are not characteristic but gradually crystallize into an unmistakable pattern. Headache, malaise, anorexia, slight elevation of temperature may be the only signals of the impending catastrophe. Vomiting is an early feature, but is not persistent; abdominal pain and diarrhea are of variable occurrence. Central nervous system signs are not prominent until later. Likewise in our experience, the birth, developmental, and familial histories were non-contributory. The onset was sudden, accompanied in 5 cases by vomiting and variously involving headache, abdominal pain, fever, cyanosis, and convulsions as the chief complaint. We wish to draw attention to the history of 1 of our patients whose mother stated that "the rash was not present when the child left the house for the hospital." This diagnostic statement was first recorded by Blaher and Bailey³ and later by Brown.⁴

Within 8 to 12 hours of the onset a striking cyanosis occurs, this being generally the first sign which brings the patient to the hospital. Sacks¹⁷ notes that the cyanosis was present in 46% of the cases and varied from a deep blue involving both the lips and nails to an alternation of cyanosis with pallor, which occurred in 2 cases; Magnusson¹⁴ states that this phenomenon when present in an acutely ill child is diagnostic. Following the cyanosis, petechial mottling of any part of the body appears; the appearance is characteristic and as the hemorrhages involve more and more of the skin area, the body surface assumes the postmortem lividity described by Aegerter.¹ Weak irregular heart action and peripheral collapse are more likely to supervene as the condition of the patient becomes more critical. Concomitantly with the appearance of the rash, or shortly following, the individual becomes moribund or stuporous and this condition persists until death occurs.

Initial examination reveals an acutely ill child, the respirations and pulse always being rapid. The temperature is characteristically septic and may vary from 98° to 108° F., but in the majority of instances is above 103° F.

An examination of the temperature charts of our patients reveals the following pertinent data:

	<i>Temperature.</i>	<i>Pulse.</i>	<i>Respiration.</i>
High	107.0	156.0	48.0
Low	99.0	136.0	40.0
Average	104.2	144.4	42.5

The extremities are generally cold, the body hot, and this peripheral circulatory failure has been said not to occur until the adrenal damage has taken place. The heart and lungs reveal little beside a moderate number of basal moist râles. The abdomen is negative.

TABLE 1.—CLINICAL DATA IN 7 CASES OF WATERHOUSE-FRIDERICHSEN SYNDROME.

Case.	Age (yrs.), Sex, Race.	Duration of illness.	Admitting diagnosis.	Treatment.	History.	Physical examination.	Blood examinations.
J. C. 11/29/35	2½ W. F.	15 hrs. 5 mins.	Tonsillitis Possible: (1) Meningitis (2) Purpura hemorrhagica	Oxygen Amytal Lumbar puncture Caffeine Adrenaline	Awoke at night and vomited; 5 hrs. later purpura appeared, and 4 hrs. following, convulsions occurred	T. 105° F.; P. 140; R. 40 Good nutrition; acutely ill; neck rigid; naso-pharyngitis; generalized purpura	W.B.C. 12,000; 52% neutrophils
D. M. 12/9/35	3 W. M.	48 hrs.	(1) Purpura (2) Septicemia (3) Meningitis	Oxygen Caffeine Adrenaline Coramine	Physician stated that a convulsion occurred 40-48 hrs. prior to admission	T. 99.4° F. Good nutrition; moribund; pharyngitis; heart action irregular, poor quality; generalized purpura	
E. R. 3/22/36	6 C. M.	17 hrs. 25 mins.	Not made	Lumbar puncture Coramine Adrenaline Transfusion	Headache, vomiting, fever, delirium; rash not present when patient left home for hospital	T. 106° F. Good nutrition; acutely ill; naso-pharyngitis; ptosis of left eyelid; petechiae over face; spinal fluid—suggestion of cloudiness	
R. S. H. 3/25/36	1 W. M.	12 hrs. 30 mins.	(1) Blood dyscrasia (2) Epidemic meningitis (3) Resolving pneumonia	Oxygen Adrenaline Coramine Calcium gluconate Transfusion	Vomited, 6 hrs. later purpura hemorrhages appeared on face, later over legs	T. 104.6° F. Fair nutrition; acutely ill, cervical and axillary adenopathy; naso-pharyngitis; lungs: left, crepitant and subcrepitant râles; liver palpable; generalized purpura; spinal fluid clear	Hemoglobin 11.48 gm.; R.B.C. 4,550,000/c.mm.; W.B.C. 12,200/c.mm.; 58% neutrophils; platelets 110,000/c.mm.
L. C. 5/16/36	5 C. M.	16 hrs. 40 mins.	Waterhouse-Friderichsen syndrome	Adrenaline Eseratin Meningococcus antitoxin Transfusion	Coryza for 1 wk.; abdominal pain, vomiting and chills	T. 103.6° F.; P. 140; R. 43 Fair nutrition; acutely ill; naso-pharyngitis; hyperesthesia, positive Kernig and Brudzinski; purpura coalescing	Hemoglobin 11.48 gm.; R.B.C. 5,440,000/c.mm.; W.B.C. 23,500/c.mm.; 76% neutrophils; platelets 330,000/c.mm.; bleeding time 3½ mins.; coagulation time 3½ mins.
R. S. 8/23/37	5½	14 hrs. 25 mins.	Undetermined	Oxygen Coramine	Pain in chest and vomiting, 6 hrs. later became comatose	T. 107° F.; P. 156 Comatose; pharyngitis; heart action weak; extremities cold, body hot	Hemoglobin 12.92 gm.; R.B.C. 4,260,000/c.mm.; W.B.C. 7800/c.mm.; 42% neutrophils; CO ₂ combining power 12 vol. %; N.P.N. 52 mg. per 100 cc.; sugar 76 mg. per 100 cc.
H. P. 1/4/38	1 W. M.	13 hrs. 30 mins.	Meningococcal septicemia Bronchopneumonia Septicemia	Oxygen	Rhinopharyngitis for 2 wks.; fever and cyanosis this A.M.	T. 104° F. Good nutrition, acutely ill; naso-pharyngitis; generalized purpura	

Neurologic examination gives variable results. Less common findings, as listed by Aegerter,¹ include muscle flaccidity, tremor, chills, strabismus, convulsions and rigidity of the abdominal muscles. Cyanosis and purpuric hemorrhages were present in all of our cases. Physical examination revealed variable findings, although the presence of an injected pharynx and hypertrophied reddened tonsils were noted in all.

Laboratory examination may not be helpful. Leukocytosis should occur but the majority of the patients expire before adequate examination can be performed. Lumbar puncture is of value in direct relation to the progress of the condition; abnormal findings are generally present shortly before death. Smear and culture of purpuric skin areas, as suggested by McLean and Caffey¹² will, in our opinion, prove of value in a majority of the cases. This procedure has not been used extensively in the syndrome under discussion. Bamatter,² who states that low blood sugar values are pathognomonic of this disease condition, nevertheless concludes that the converse may be true as evidenced in his own case report. Magnusson¹⁴ has also reported low blood and spinal fluid glucose values and feels that, in other conditions, even shortly before death, the blood sugar is maintained at a normal value.

The average white blood cell count which we obtained was 13,875, of which 57% were neutrophils. The thrombocytes were estimated in only 2 cases, averaging 220,000. In 1 case, blood findings included sugar 76 mg. per 100 cc., non-protein nitrogen 52 mg. per 100 cc., and carbon dioxide combining power 12 vol. %. The spinal fluid varied in cellular content from 6 to 202 cells and averaged 82 cells in the five fluids which were examined before death; the neutrophils averaged 64%.

Pathology. Bilateral adrenal hemorrhage has occurred in 95 % of the reported cases, according to Aegerter.¹ These findings vary from petechial hemorrhages to bleeding, converting the organ into a "blood cyst." When the bleeding was mild in degree it was generally stated that the medulla was more involved than the cortex, and that the right adrenal was more often damaged than the left. Various theories have been advanced as to the causation. Among the possibilities suggested by Firor⁷ are: 1, venous thrombosis; 2, toxins causing an increased permeability with rupture of the venous walls; probably bacterial embolism is a factor. Why the adrenals are more vulnerable than other tissues cannot be answered but possibly the biologic action of the gland or a relative increase in blood flow through these veins may be the answer. We feel that the combination of venous thrombosis and an increased permeability due to toxins from virulent organisms lodged in the vessels may explain the majority of cases. Sacks¹⁷ stated that the involvement of the skin and adrenal medulla, both of similar ectodermal origin, is an evidence of the ectodermal tropism of the meningococcus.

TABLE 2.—AUTOPSY FINDINGS IN 7 CASES OF WATERHOUSE-FRIDERICHSEN SYNDROME.

Case.	Thymus (gm.).	Brain.	Mediastinal and bronchial nodes.	Spleen (gm.).	Mesenteric nodes.	Adrenals.	Spinal fluid.	Heart's blood culture.
J. C.	38.0	Not examined	Reddened and enlarged	Normal	Reddened and not enlarged	Right 5 gm., left 9.5 gm.; dark mahogany, due to hemorrhage	Cell count 6; neutrophils 50%; globulin increased; sugar normal; culture <i>Neisseria intracellularis</i>	<i>Neisseria intracellularis</i>
D. M.	39.0	Edematous and soft; extensive greenish-yellow exudate	No note	200.0 (Normal 37.0)	Not enlarged	Both markedly hemorrhagic	Cell count 1420; neutrophils 50%; globulin increased; sugar decreased; culture <i>Hemophilus influenzae</i> , postmortem	<i>Hemophilus influenzae</i>
E. R.	27.0 Petechial hemorrh.	Some swelling; no definite exudate	Reddened and prominent	Normal	Red and prominent	Both markedly hemorrhagic	Cell count 202; neutrophils 98%; culture <i>Neisseria intracellularis</i> postmortem	<i>Neisseria intracellularis</i>
R. S. H.	28.5 Reddened	Meninges congested; convulsions moderately flattened	Prominent due to marked congestion	28.0	Prominent due to hyperplasia and occasional hemorrhage	Right 4 gm., left 4 gm.; hemorrhage scattered throughout medulla and cortex; periaxonal tissue has an edematous and grayish-mucoid appearance	Cell count 33; neutrophils 77%; culture <i>Neisseria intracellularis</i>	<i>Neisseria intracellularis</i>
L. C.	18.0	Meninges show a moderate hyperemia; convulsions moderately flattened	Hyperplastic and enlarged	Slightly larger than normal; follicles prominent	Hyperplastic	Right 4 gm., left 4 gm.; right is dusky red injected, no gross hemorrhage; left moderate hemorrhage into cortex	Cell count 87; neutrophils 75%; globulin increased; sugar normal; smear and culture <i>Neisseria intracellularis</i>	<i>Neisseria intracellularis</i>
R. S.	41.0	Increase in cerebrospinal fluid as indicated by the edematous appearance of the pia-arachnoid	No note	63.0 (Normal 52.0)	Slightly enlarged	Right, periaxonal edema and hemorrhage into the organ; left, considerable hemorrhage	Cell count 293; neutrophils 62%; culture <i>Neisseria flava</i> II, postmortem	<i>Neisseria flava</i> II <i>Alcaligenes faecalis</i>
H. P.	23.2 Petechial hemorrh.	Moderately edematous; slight exudate on surface	Enlarged, hemorrhagic and soft	37.5 (Normal 17.0)	Slightly enlarged	Right, not weighed; left, 4.5 gm.; deep maroon due to hemorrhage, infiltrated throughout	Cell count 986; neutrophils 87%; culture <i>Hemophilus influenzae</i> postmortem	<i>Hemophilus influenzae</i>

Rabinowitz¹⁶ and Bamatter² have drawn attention to the prominence of the thymolymphatic system in those who succumb to this infection. In our 7 cases the thymus varied in weight from 18 to 41 gm., averaging 30.7 gm., displaying petechial hemorrhages in 4 cases. In 4 patients the bronchial and mediastinal nodes were enlarged and hemorrhagic; in 6 the prominence and redness of the mesenteric lymph nodes was notable. The spleen was definitely enlarged in 3 cases. The relation of these findings to the rapid exitus leads to interesting speculative possibilities. That these prominent lymphoid structures may regress rapidly is a known fact; whether they may attain a similar prominence from a former normal state is an unknown, but interesting possibility. Whether the controversial status thymolymphaticus enters into this picture may excite some comment, but the definite relation of these findings to this disease condition remains unknown.

Postmortem findings in the other viscera are not remarkable, varying widely in different cases.

Etiology. Although numerous investigators have suggested that the meningococcus may be the sole cause of this syndrome, we wish to point out that our experience does not lead to such a conclusion. In 2 of our cases the organism, as isolated from both the hearts' blood and cisternal fluid, proved to be the *Hemophilus influenzae* and in another, *Neisseria flavus II* was present.

Although the isolation of organisms from these cases proved to be of great difficulty to early investigators, Dudgeon,⁶ in 1904, found *Staph. aureus* in 1 case and pneumococcus in another. It seems quite possible that the pneumococcus represented the etiologic organism in that particular case. Both Mair¹⁵ and Julianelle and Reimann⁹ have reported on the ability of the pneumococcus to produce purpuric skin lesions and on the epithelial tropism of this organism.

Although the meningococcus is by far the most frequent offender, the only other organism obtained with any frequency being the *Strep. hemolyticus* (Snelling and Erb, quoted by Sacks¹⁷), it must be borne in mind that this organism does not represent the sole etiologic factor in all cases. It is our opinion that with proper technique and precautions the responsible organism will be recovered in the majority of cases.

Treatment. Since the diagnosis must be corroborated by post-mortem observation, it is obviously difficult to evaluate the effect of adequate therapy. However, it is our belief that in the presence of a patient in whom a tentative diagnosis is ventured, treatment should be instituted immediately. According to the pathology, this should theoretically consist of: 1, measures to combat the invading organism; 2, measures to combat the suprarenal damage; and 3, supportive treatment.

We feel that the *Neisseria meningitidis* is responsible for the majority of cases and that the *Hemophilus influenzae* may account

for the greater proportion of the remainder; consequently, when the invader is not immediately identified, it is logical to assume the presence of either of the two above-mentioned pathogens. In that case, antimeningococcus antitoxin should be administered by the intravenous route and anti-influenzal serum intramuscularly.

Although sulfanilamide has been favored at this writing by the majority of investigators, it is possible, judging from recent reports, that sulfapyridine will replace it as the drug of choice; we therefore recommend its administration in adequate dosage, first intravenously in the form of the soluble sodium salt, later *per os*.

Both epinephrin and cortin or desoxycorticosterone should be supplied in the desperate effort to maintain the somatic equilibrium; sodium chloride should also be given. Intravenous glucose and blood transfusion are also necessary therapeutic adjuncts.

Due to the fulminant character of this malignant infection, an immediate supply of the above-mentioned defense factors is an essential if we hope to reduce the present 100% mortality. Carey⁵ has recently reported a case of recovery in a 27-year-old white female, although therapy was not instituted for approximately 21 hours after the onset of symptoms; his success in an apparent case of this nature is encouraging.

Comment. Attention is drawn to the ease of diagnosis of the Waterhouse-Friderichsen syndrome if the condition is kept in mind. In the presence of a previously well, but critically ill child, without localizing signs, this disease complex must be considered. The clinical course will corroborate or disprove the diagnosis; in the meantime, laboratory facilities may enable this clinical diagnosis to be confirmed and appropriate therapy instituted.

With other investigators, we strongly urge that future studies endeavor to correlate the known thymolymphatic prominence of the individuals who succumb to this disease and its possible relationship to the peculiar pathogenesis.

It is interesting to note that the statistics of this hospital reveal that influenzal meningitis occurs as frequently as meningococcic meningitis if epidemic periods be eliminated. Thus, it would seem that future investigators may find *Hemophilus influenzae* in a similar proportion of this syndrome as an etiologic agent.

Speculative, also, is the fact that of the total 89 cases reported thus far, 30 had been published by 1904. Whether the following dearth of similar reports was due to a scarcity of such cases, decrease in virulence, or lack of recognition is not known; however, the latter possibility seems to be the most likely.

Conclusion. Seven cases of acute bilateral suprarenal hemorrhage are reported.

The bacteriologic offender was identified in each instance; four infections were attributed to *Neisseria meningitidis*, two to *Hemophilus influenzae* and one to *Neisseria flavus* II.

We feel that the syndrome occurs more frequently than is now

estimated. In the presence of an illness of apoplectic onset in a previously well infant the appearance of alternate pallor and cyanosis or purpura, peripheral collapse, or hypoglycemia may well suggest the diagnosis.

It is felt that the prominence of the thymolymphatic apparatus in victims of this infection is worthy of investigation.

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THE CEREBROSPINAL FLUID TOTAL PROTEIN IN THE ALCOHOLIC PSYCHOPATHIES.

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THIS study resulted from the observation that the cerebrospinal fluid total protein was abnormally elevated in several patients suffering from such alcoholic psychopathies as delirium tremens and Korsakow's psychosis. These findings were rechecked, and after ruling out other possible contributory factors, it was felt that further investigation was warranted in view of the significance of elevated total proteins in other conditions affecting the central nervous system. A review of the rather meager literature on this problem revealed some suggestive but generally non-confirmatory material. Bargues and Berthon¹ reviewed several series of cases. They cite Villaret who reported increased cerebrospinal fluid albumin in only

2 of 12 cases of delirium tremens. This work was done in 1910, 10 years before the development of more accurate methods for quantitative determination of total proteins. They include Abadie and Pauly's series of 33 cases of chronic alcoholism with mental complications, in which only 39% showed a definite "hyperalbumose." They also report a series studied by Mele and Truck in which 40% of cases showed a slightly increased protein. Courtois and Picard³ examined the cerebrospinal fluid total protein in 87 cases of simple alcoholism, 9 cases of alcoholism with "épilepsie toxique" and 4 cases of Korsakow's psychosis. In this series only 1 case in the second group was above 40 mg. per 100 cc. Eight cases in the first group had values over 30 mg. per 100 cc. while none of the Korsakow psychoses were at all normal. Neel¹³ found above normal values in 142 of 209 cases of chronic alcoholism. Unfortunately the percentage of mental complications was not noted.

The above material did not seem to be adequate both because of the paucity of cases and the questionable validity of the procedures employed. The following investigation was then undertaken in an attempt to demonstrate whether or not the cerebrospinal fluid total proteins in the alcoholic psychopathies were increased consistently enough to be statistically significant.

Method. The present series consisted of 102 consecutive cases of alcoholism admitted to the Psychiatric Division of the Albany Hospital. The diagnosis of alcoholism, with or without psychopathy, was made at all times in concurrence with the opinion of the psychiatric staff members. Lumbar puncture was done within 48 hours of admission. Total proteins were determined* by the nephelometric method of Dennis and Ayer⁵. Both leukocyte and erythrocyte counts were done on the same specimen within 2 hours after puncture. Cerebrospinal fluids containing erythrocytes were not included in the cases statistically studied as it was found that as few as 10 to 30 erythrocytes per c.mm. produced erroneous protein values and frequently gave a positive Pandy reaction. Cases which subsequently revealed concomitant central nervous system disease such as neurosyphilis, multiple sclerosis, cerebral concussion, idiopathic epilepsy or psychosis with cerebral arteriosclerosis were omitted.

Results. Table 1 presents the data on cases with cerebrospinal fluid total proteins of 40 mg. per 100 cc. and below. Table 2 does likewise with values above 40 mg. per 100 cc. Forty-two cases in the first category gave an average total protein of 31.9 mg. per 100 cc., with values ranging from 14.1 to 40 mg. per 100 cc. Sixty cases comprising the second group averaged 58.6 mg. per 100 cc. of total protein with values ranging from 40.3 to 118 mg. per 100 cc. Of the 60 cases having total proteins of over 40 mg. per 100 cc., 43 cases (71.6%) had definite direct or indirect central nervous system complications of alcoholism. Of the 42 cases with values of 40 mg. per 100 cc. and below, 10 cases (24.2%) had central nervous system complications. Table 3 gives an analysis of the

* Total protein determinations were made by the Department of Biochemistry of the Albany Medical College.

different alcoholic psychopathies encountered, totalling 53 cases with an average total protein of 52.8 mg. per 100 cc. The 49 cases of uncomplicated alcoholism averaged 37.7 mg. per 100 cc. Cerebrospinal fluid cytology was not significant, only 8 cases having leukocyte counts over 10 cells per c.mm.

TABLE 1.—SPINAL FLUIDS WITH TOTAL PROTEINS OF 40 MG. PER 100 CC. AND BELOW IN ALCOHOLICS.

Patient.	Age.	Sex.	Duration of alcoholism.	Associated mental state	Total protein, mg. per 100 cc.
1. A. G.	40	F	3-5 yrs.	?Paranoid schizophrenia	36.7
2. J. L.	42	M	10-15 yrs.	None*	30.4
3. R. W.	51	M	"Social drinking"	?Paranoid reaction	32.8
4. F. W.	29	M	3-4 mos.	Polyn neuritis	30.0
5. R. P.	56	M	15-20 yrs.	None	35.0
6. F. C.	52	M	15-20 "	Mild CO poisoning	35.7
7. W. Mc.	44	M	10 "	None	30.2
8. M. K.	42	M	10 "	None	33.7
9. A. W.	48	M	5 "	None	21.5
10. W. H.	46	M	20 "	?Lateral sclerosis	35.7
11. A. S.	35	M	3 "	None	22.5
12. E. L.	45	M	20 "	None	33.8
13. E. K.	40	F	3 "	None	24.5
14. W. G.	52	M	20 "	None	35.7
15. E. G.	29	F	4 "	None	32.0
16. F. T.	47	M	15-20 "	Polyn neuritis	32.4
17. L. H.	28	M	6 "	Catatonic schizophrenia	36.0
18. F. G.	34	M	"Social drinking"	None	31.2
19. W. W.	27	M	"Social drinking"	None	20.7
20. H. C.	41	M	10-15 yrs.	Delirium tremens	23.8
21. J. C.	37	M	6 "	None	30.0
22. J. Mc.	42	M	25 "	Mild confusion	22.0
23. C. R.	41	M	3 "	Delirium tremens	30.8
24. J. P.	42	M	15 "	None	26.0
25. E. R.	40	F	10 "	None	23.8
26. L. D.	38	F	5 "	Overactive at times	14.1
27. J. B.	42	M	? "	None	32.0
28. J. B.	33	M	? "	None	39.2
29. F. H.	38	M	? "	Transitory confusion	27.4
30. W. N.	43	M	4 "	Convulsive, hypertension	36.0
31. W. M.	46	M	20 "	Epileptiform seizures	25.0
32. H. H.	24	F	4-5 "	Acute hallucinosis	29.4
33. E. S.	38	M	8-10 "	Slight tremor	38.1
34. C. W.	39	M	5 "	None	31.6
35. K. Mc.	31	M	5 "	Acute hallucinosis	38.1
36. A. G.	21	M	8-10 mos.	None	31.2
37. F. Mc.	40	M	10 yrs.	Depressive state	39.6
38. G. M.	52	M	3-5 "	Epileptiform seizures	40.0
39. W. F.	33	M	6 mos.	None	28.7
40. W. G.	39	M	7-8 yrs.	None	27.0
41. F. G.	48	M	10-15 "	Paranoid reaction	33.0
42. H. B.	34	M	5-6 "	None	55.5

* "None" indicates acute alcoholic intoxication limited to 48 hours.

Discussion. The findings indicate a definite tendency for the cerebrospinal fluid total proteins to be pathologically increased in the alcoholic psychopathies. The statistical support for this contention is obvious even after allowance is made for the fact that the method used has a possible technical error of 10%. The Dennis-Ayer method used in this work has been generally accepted and regarded as quite reliable. Brown, Gildea and Man² compared this procedure with two Kjeldahl methods and found agreement within 12 mg. per 100 cc., the Dennis-Ayer method always giving the lowest values.

Total protein values above 40 mg. per 100 cc. were regarded as indicating pathologic increase. That this somewhat arbitrarily chosen dividing line is not too low is supported by the work of numer-

TABLE 2.—SPINAL FLUIDS WITH TOTAL PROTEINS ABOVE 40 MG. PER 100 CC. IN ALCOHOLICS.

Patient.	Age.	Sex.	Duration of alcoholism, (yrs.).	Associated mental state.	Total protein, mg. per 100 cc.
1. C. W.	49	F	20	Dipsomania	48.2
2. K. F.	41	M	10-15	Delirium tremens	55.5
3. E. S.	41	F	10-15	Atypical Korsakow's psychosis	40.3
4. J. A.	67	M	20	Hallucinations, delusions	45.0
5. C. F.	66	F	20	?cerebral arteriosclerosis	46.5
6. C. C.	55	M	20	Depressed state	61.5
7. B. T.	65	M	20	Convulsions	73.0
8. F. H.	45	M	2	Bilateral optic neuritis	44.0
9. N. Mc.	39	M	10(?)	Delirium tremens	52.0
10. P. Mc.	47	M	20	Delirium tremens	63.5
11. P. D.	31	M	6	Depressed state	68.0
12. O. P.	51	M	25	Confused, disoriented state	72.7
13. G. H.	63	M	20	Delirium tremens	66.6
14. F. O'H.	55	M	25	Paranoid reaction	72.7
15. T. H.	66	M	25	Confused state	49.4
16. J. S.	33	M	3-4	Depressed state	53.3
17. T. M.	53	M	2-3	Delirium tremens	50.6
18. G. J.	50	M	20	Manic delirium	50.0
19. W. Mc.	50	M	10-15	Convulsive state	61.5
20. J. S.	38	M	12	Delirium tremens	48.2
21. R. B.	41	M	18	Delirium tremens, polyneuritis	95.0
22. B. K.	34	M	10-15	None (formerly had neurosyphilis)	71.4
23. J. W.	52	M	20	Comatose state (20 hours)	62.5
24. C. P.	50	M	10-20	None	45.0
25. H. W.	48	M	30	Confusion, tremors-polyneuritis	50.0
26. R. J.	37	F	16	Delirium tremens	45.5
27. E. D.	35	M	12	None	45.5
28. H. T.	56	M	30	Delirium tremens	44.4
29. B. S.	56	F	25	Toxic psychosis ?bromidism	53.3
30. J. W.	52	M	20	Comatose state (24 hours)	62.5
31. M. Mc.	51	F	10	Depressed state ?menopausal syndrome	46.0
32. R. L.	39	M	7	Manic delirium	46.5
33. M. G.	54	M	20	Paranoid reaction	64.5
34. L. C.	52	M	20	Delirium tremens	40.4
35. J. M.	25	M	5	None	48.7
36. J. Z.	54	M	30	Delirium tremens	62.5
37. M. W.	37	F	10	Polyneuritis-overactivity	50.0
38. E. L.	31	M	5	Comatose state (10 hours)	52.0
39. J. G.	50	M	20	Korsakow's psychosis	47.6
40. J. H.	39	M	10-15	Acute hallucinosis	48.7
41. M. Mc.	32	M	2½	Depressed, anxiety state	72.7
42. A. R.	30	M	5	Convulsive state	64.5
43. H. W.	48	M	15-20	None	45.5
44. B. L.	38	M	13	Psychopathic personality	50.0
45. J. D.	42	M	15	Reactive depression	59.0
46. E. W.	38	M	10	Reactive depression	50.0
47. M. G.	42	F	10	Paranoid reaction	49.4
48. J. H.	38	M	15-20	Delirium tremens	118.0
49. J. F.	39	M	5-10(?)	None ?head trauma	59.4
50. M. L.	35	F	10	Delirium tremens	55.5
51. W. Mc.	31	M	10	Manic delirium	57.0
52. J. S.	40	M	15	Korsakow's psychosis	46.0
53. A. K.	42	M	10-15	Comatose state (15 hours)	65.5
54. J. O.	49	M	10-15	Korsakow's psychosis*	80.0
55. J. K.	45	M	20	Delirium tremens	74.0
56. W. W.	39	M	10-15	Epileptiform seizures	42.1
57. P. K.	46	M	20	Convulsive state (3 years)	75.0
58. E. S.	45	M	15-20	Delirium tremens	75.5
59. G. M.	62	M	15-20	Korsakow's psychosis*	106.0
60. B. M.	39	M	10-15	Korsakow's psychosis	69.0

* Memory loss, confabulation, disorientation present but polyneuritis absent.

ous investigators. Kafka,⁹ using both Kjeldahl and Esbach techniques, found average values in normals to be 24 mg. per 100 cc. Phillips¹⁶ (method not stated) offers normal values ranging from 20 to 40 mg. per 100 cc. Schube¹⁷ prefers to consider normal range between 0 and 39.99 mg. per 100 cc. He quotes 22 writers employing different methods, 18 of whom found normal values definitely less than 40 mg. per 100 cc., 3 observed normal range from 17 to 50 mg. per 100 cc., while 1 felt that the diversity of normal values was much greater, namely, 35 to 100 mg. per 100 cc.

TABLE 3.—ANALYSIS OF DATA.

Alcoholic psychopathies.	Cases with total protein over 40 mg. per 100 cc.	Cases with total proteins of 40 mg. per 100 cc. and below.	Average total proteins, mg. per 100 cc.
1. Acute hallucinosis	2	2	42.9
2. Delirium tremens	15	2	58.3
3. Confusion with polyncuritis	3*	2†	41.3
4. Paranoid reaction	3	3	48.2
5. Korsakow's psychosis	6	0	55.6
6. Convulsive states	5	0	64.7
7. Manic delirium (without tremor)	5	1	51.1
8. Comatose, stuporous states	4	0	60.6
Totals	43	10	52.8‡

* One case was predominantly an optic neuritis.

† These 2 cases presented very little psychopathology.

‡ Average total protein in all cases of central nervous system complications of alcoholism.

Assuming then that the results do show an abnormal increase of cerebrospinal fluid total protein in the alcoholic psychopathies, what does this signify? Before attempting to answer this question it is necessary to clarify our concepts with respect to several points, namely, the origin of normal cerebrospinal fluid total protein, the significance of so-called pathologic values of total protein in other central nervous system diseases, the relationship of total protein to the permeability of the hemato-encephalic barrier, and finally, the significance of barrier permeability in lesions of the central nervous system. Complete knowledge on these several aspects of the problem is lacking, but some work has been done which offers suggestive leads for further study.

Authorities⁸ state that under normal conditions blood plasma proteins do not penetrate the semipermeable membrane or hemato-encephalic barrier which separates the cerebrospinal fluid system from the blood stream. It is felt that the small amount of protein normally present is derived from the usual catabolism of the tissues of the central nervous system, although nothing seems to be known about the mechanism which prevents this material from eventually accumulating, provided of course that the original assumption is accurate. In pathologic conditions the protein is frequently abnormally elevated. Here, too, the source of protein increment is as yet an open question. Malamud, Miller and Mullins¹² rest the

matter in a choice between a hematogenic or a central nervous system destructive process. Schube¹⁷ expresses the same viewpoint, adding that the hematogenic mechanism may be a direct transudation through dilated meningeal vessels. Thompson *et al.*¹⁹ point out that cerebrospinal fluid protein is high in myxedema and questions the possible relationship of this finding both to the storage of nitrogenous substances and the frequent albuminuria which are present in myxedema. This observation favors the hematogenic theory. Deane⁴ states that generalized increased intracranial pressure *per se* such as occurs in internal hydrocephalus does not increase the protein, but notes that the increased protein frequently found in intracranial tumors is caused by local compression of relatively non-anastomotic venous channels draining the choroid plexuses, especially in the lateral and third ventricles. He regards the choroid plexuses as the sites whence at least the major quantity of protein gains access into the cerebrospinal fluid in normal individuals and in cases of intracranial tumors.

It is known that increased protein in certain central nervous system diseases (neurosyphilis, meningitis, encephalitis) is frequently a crude indicator of the extent of the disease process, progress in the condition often being paralleled by the protein curve. On the other hand, this relationship does not hold in a number of other conditions such as paralysis agitans, multiple sclerosis, or idiopathic epilepsy. In epilepsy, Patterson and Levi¹⁵ studied the proteins in 50 cases and found values unchanging and consistently under 30 mg. per 100 cc. The writer has found in an unpublished study of a series of organic psychoses of the senium that, although the cerebrospinal fluid protein was frequently elevated, repeated punctures done on subsequent occasions when the patients were improved, unchanged or worse failed to show a sufficiently significantly positive correlation between the protein curve and the clinical course. Apparently a consistent relationship between protein and all forms of central nervous system disease cannot be demonstrated. One gets the impression, however, that elevated protein points rather definitely to the presence of tissue lesions. Fremont-Smith *et al.*⁶ sum up the situation with the statement that "values between 45 and 60 mg. per 100 cc. in the large majority of cases accompany central nervous system pathology."

Hemato-encephalic barrier permeability studies give additional meaning to the question of protein significance. Nicolajev,¹⁴ Katzenelbogen¹⁰ and Stern and Lokschina¹⁸ among others point out that barrier permeability is increased in the majority of cases in which cerebrospinal fluid total protein is elevated. It is interesting to note that Malamud *et al.*¹² found that while the correlation between protein and barrier permeability quotient is not highly consistent as studied in manic-depressives, schizophrenics, psychoneurotics and a fourth group consisting of toxic and organic psychoses (cere-

bral arteriosclerosis and general paresis), the highest correlation occurred in the toxic-organic group.

The normal constancy of barrier permeability is regarded as the keystone in the defence which the central nervous system possesses against systemic invasion by disease processes. This barrier can be weakened by certain toxic agents and there is evidence to prove that one of these is alcohol. Gabriel, Palisa and Novotny⁷ found in a series of cases of delirium tremens that the cerebrospinal fluid alcohol content was abnormally present in 45.3%. Furthermore they noted that the blood alcohol frequently returned to normal while the cerebrospinal fluid alcohol still remained high. Stern and Lokschina¹⁸ tested barrier permeability on rabbits and guinea pigs subjected to acute and chronic alcohol poisoning. In acute brief intoxication experiments no change was found in the normal resistance to the passage of colloids. In chronic alcohol poisoning, however, a definite increased permeability for colloids was demonstrated. That alcohol also exerts a histotoxic action on nerve tissue itself is postulated by McFarland and Barach,¹¹ who claimed that the histotoxicity leads to a state of anoxia. They tested out this theory by giving severe alcoholic cases inhalations of a mixture consisting of 50% oxygen and 10% carbon dioxide. They found that both blood alcohol and blood lactic acid were drastically lowered with concomitant improvement in mental and motor behavior.

Conclusions. Evidence is presented to show that the alcoholic psychopathies in the great majority of instances are associated with elevated cerebrospinal fluid total protein. The literature strongly suggests that the alcoholic psychopathies are closely associated with a direct toxic effect of alcohol upon the central nervous system and that this action very frequently results in a pathologic increase of cerebrospinal fluid total protein. Part of this protein seems to be derived from the systemic circulation due to increased permeability of the hemato-encephalic barrier, while the remainder appears to result from pathologic central nervous system tissue catabolism. The normal protein values found in the 24.2% of cases in this series which showed alcoholic psychopathy cannot be accounted for except on the basis of individual variation in either nervous tissue or barrier permeability resistance.

Summary. 1. Cerebrospinal fluid total protein was determined on 102 consecutive cases of alcoholism.

2. Pathologic total protein values were found in 71.6% of all cases in which psychopathy was present.

3. The literature on the cerebrospinal fluid total protein in the alcoholic psychopathies was surveyed and the significance of the findings was discussed.

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USE OF ACETYL-BETA-METHYLCHOLINE CHLORIDE IONTOPHORESIS IN NON-ARTERIAL PERIPHERAL VASCULAR DISEASE.

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THERE are several favorable reports of the treatment of varicose ulcers,^{4b,10} thrombophlebitis with and without ulceration,^{9,11} and scleroderma³ by iontophoresis with acetyl- β -methylcholine chloride. Kovacs first described the procedure and suggested the technique which has since been followed. Baker¹ recently had less favorable results in the treatment of a short series of patients having varicose ulcers, and more favorable results with older and simpler methods.

The present paper deals with the results of treating 42 patients by acetyl- β -methylcholine chloride iontophoresis in the Peripheral Vascular Clinic from October, 1937, to August, 1940. Kovacs^{4a} method was used, with the sole exception that 0.2% acetyl- β -methylcholine chloride* instead of 0.5% was used, since the difference in effect was indistinguishable clinically, and since experimental data bear out this clinical impression.⁸ Any one patient received from 2 to 217 treatments: fewer than 10 treatments were considered an inadequate trial but all patients are reported (See Table 1). When the patient could tolerate it 20 to 30 milliamperes of current were used for 20 to 30 minutes, but the whole range was 5 to 30 milliamperes for 5 to 40 minutes.

Ten of the 42 patients had varicose ulcer, 6 post-thrombophlebitic ulcer, 11 chronic or subacute thrombophlebitis without ulcer, 6

* Merek & Co. kindly supplied the acetyl- β -methylcholine (Mecholyl) and special asbestos paper for iontophoresis.

TABLE 1.—SUMMARY OF CASES TREATED WITH ACETYL- β -METHYLCHOLINE IONTOPHORESIS.

No.	Sex, Age.	Main vascular diseases.	Duration.	Previous treatment.	Previous results.	Iontophoresis.		Treatment.		Follow-up.			
						No.	Wks.	Supportive.	Results.	Time.	Treatment.	Results.	
1	F 40	Varicose Ulna. Varicose veins, ulcer	17 yrs.*	Injections, gelatin boots	Healed, recurred	20	10	Elast. band. Injections	Painless, nearly healed	1 mo.	injected vein	Healed	
2	F 61		12 yrs.*	Gelatin boots	Steadily worse	10	22	Elast. band.	Less painful, little healing	5 mos.	drained hematoma	Same	
3	F 62		30 yrs.*	Skin graft, gelatin boots	Steadily worse	13	4	Saline soaks	Still painful, no healing, asthma	2 yrs.	Gelatin boots	Better	
4	F 51		14 yrs.*	Ligations, injections, boots	Steadily worse	45	23	Elast. band.	Less painful	2 yrs.	Gelatin boots	Same	
5	M 50	Varicose veins, ulcer	4 yrs.	0	Steadily worse	5	10	Elast. band.	Moderate improvement	2 yrs.	Gelatin boots	Same	
6	F 58		22 yrs.*	Gelatin boots	Slight healing	9	23	0	0	No follow-up		Same	
7	F 48		7 yrs.*	Bandages, boots	Stationary	62	53	Elast. band.	Temp. imp., less pain	2 yrs.	Gelatin boots	Healed	
8	M 70		Many yrs.	Injections	Stationary	5	13	Elast. band.	Temp. imp., less pain	No follow-up			
9	F 60	Varicose veins, phlebitis, painful ulcer site	7 yrs.	Ligations	Worse	5	13	Elast. band.	Sl. subjective relief.	2 yrs.	Gelatin boots	Healed	
10	M 60		7 yrs.	Elastic bandages	Much worse	6	2	Elast. band.	Less pain, chills, discolor.	2 yrs.	Gelatin boots	Improved	
11	F 40		Thrombophlebitis ulcer	14 yrs.	Boots, sedatives	Steadily worse	60	20	Elast. band. Insulin	Painless, almost healed	No follow-up		
12	F 40			1 mo.	Gelatin boots	Steadily worse	2	13	Elast. band.	Less painful, too little R	No follow-up		
13	F 58	15 yrs.*		Multiple	Varying	21	7	Elast. stock.	Worse	13 yrs.	Linton oper.	Healed	
14	F 28	3 yrs.*		Supports, injections	Varying	9	3	Elast. band.	Less tender, cleaner	6 mos.	Gelatin boots	Same	
15	F 33	Thrombophlebitis ulcer, healed, painful	11 yrs.*	Supports, injections	Stationary	18	6	Elast. band.	No improvement	9 mos.	Linton oper.	Asymptomatic	
16	M 31		5 yrs.	Elastic bandage	Worse	2	1	Elast. band.	No improvement	7 mos.	Saphenous ligation	Same	
17	F 51		Other Ulcers. Decubitus ulcer, nephrolithiasis	Weeks	Incision	Worse	4	13	Back care	Sl. improvement	4 mos.	Postop. care	Healed
18	M 50			1 wk.	Back care	Sl. improved	6	13	Back care	Healed ulcer	No follow-up		
19	F 12	6 wks.		Excision, back care	Steadily worse	15	43	Back care	Steadily worse	1 mo.	No therapy	Died of infect.	

[illegible]

- Recurrent ulcers prior to iontophoresis therapy.

ulcers of other origin, 6 scleroderma, and 3 had miscellaneous disorders. Patients with occlusive arterial disease were not chosen for treatment because the results of others have not been sufficiently favorable.⁵ With one exception (Case 42, Table 1) patients with abnormal vasoconstriction were not chosen because the temporary vasodilatation afforded by acetyl- β -methylcholine chloride iontophoresis can be obtained by the simple means of heat.⁸ In most instances iontophoresis therapy of varicose ulcer and thrombophlebitis was supplemented by the use of elastic bandages. Bed rest was used only when illness had kept a patient in bed before iontophoresis was started. Otherwise no other therapy was used during the periods of iontophoresis (exception see Table 1, Case 11). When ulcers were treated they were not covered by rubber dam as advised recently by Sokolov and Meyers.¹¹

Varicose Ulcers. The initial experience with severe varicose ulcers was promising: after several treatments there was usually less pain, less odor, and some evidence of healing. Subsequently, however, there was little evidence of improvement, and not one of the ulcers healed solely as a result of iontophoresis therapy. A characteristic unfavorable response is shown in Figure 1. In 2 instances chills and fever resulted, probably from reactivation of infection from increased flow of blood through the veins. When the course of iontophoresis therapy was finished the patients were advised to have gelatin boots applied. Four of the 6 patients who had this done were further improved, 1 with healing; 2 were not improved. One other ulcer healed promptly after a vein which traversed the ulcer bed was injected with a sclerosing solution (details in Table 1).

Post-thrombophlebitic Ulcer. The results of iontophoresis therapy of ulcers developing as a consequence of previous thrombophlebitis were similar to the results in varicose ulcer. Only 1 of the 6 ulcers was markedly improved and success in that instance (Case 11, Table 1, Fig. 2a) may have come from diabetic therapy which was instituted shortly before the course of iontophoresis. A characteristic unfavorable response is shown in Figure 2b (Case 14). One of the unsuccessfully treated ulcers failed to benefit by high saphenous vein ligation and healed only after multiple ligation and section of communicating veins (Linton operation⁶). Another patient, with a painful area in the site of an old ulcer, was made symptom-free by a Linton operation (details in Table 1).

Other Ulcers. Three sacral bedsores, one ulcer in an edematous low-thigh amputation stump, one ulcer in a patient with erythema induratum and one in a patient with questionable erythema induratum and peripheral edema of cardiac origin were treated. One of the decubitus ulcers healed very promptly (Fig. 3, Case 18). The general health of this patient was improving, his activity in bed consequently was greater, and this may have contributed to the healing. Another patient's large decubitus ulcer would tolerate very little cur-

rent: it became steadily worse until the time of the patient's death 1 month later. The stump ulcer healed (Fig. 3, Case 20). Avoidance of the use of his artificial limb seemed to contribute. The ulcer

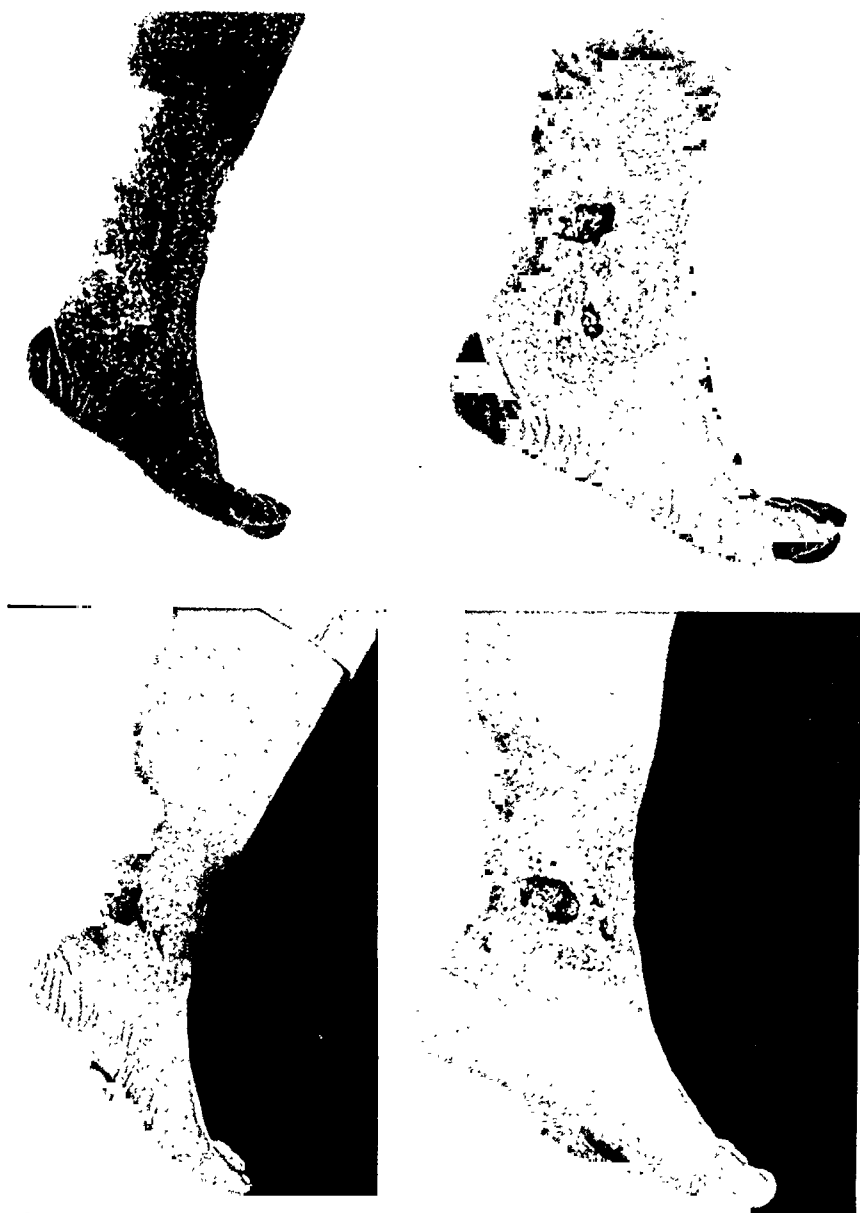


FIG. 1.—*Varicose ulcer.* Case 7. Two photographs at the left were taken 2 days after the first treatment by acetyl- β -methyleholine chloride iontophoresis; two at the right 1 month later (no improvement, ulcers less painful).

of 1 patient with erythema induratum healed (Fig. 3, Case 21); that of the other failed to heal and the patient died 1 month later of cardiac decompensation. When the third patient with decubitus

ulcer recovered from a severe urinary infection, the ulcer healed spontaneously (details in Table 1).

Thrombophlebitis without Ulcer. The results in the series of 11 patients with chronic thrombophlebitis without ulcer were fairly

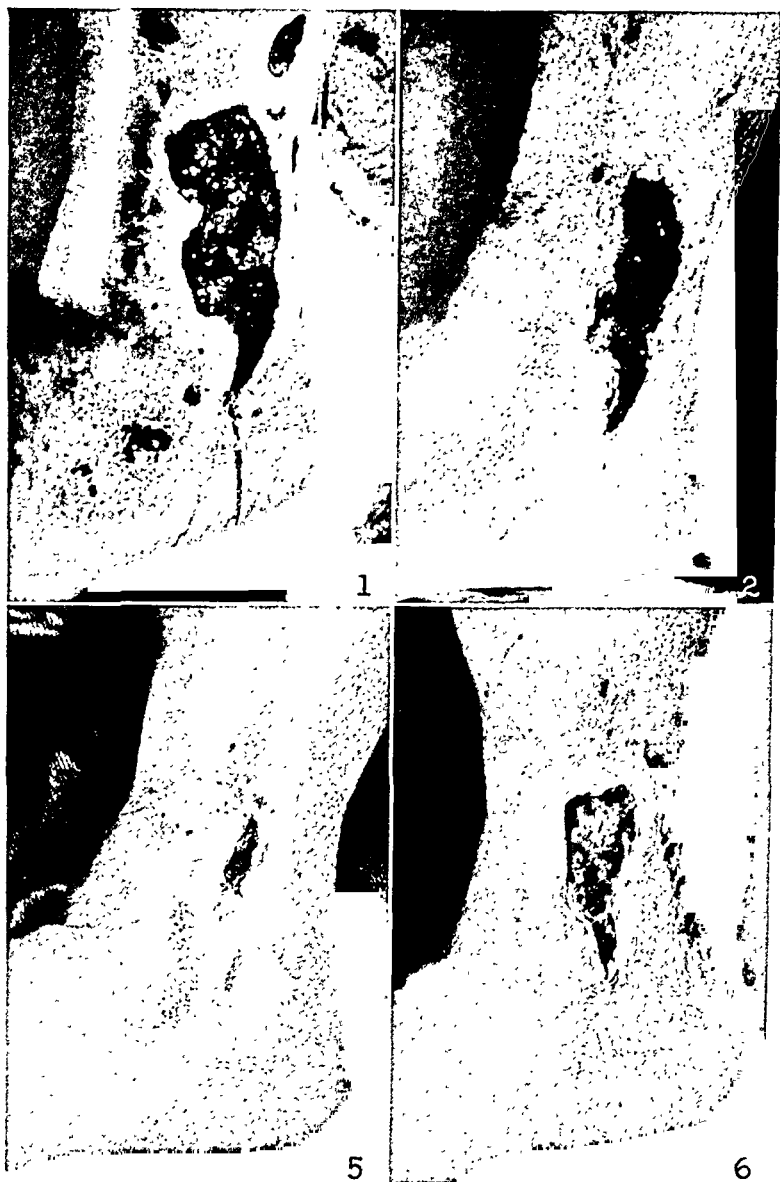
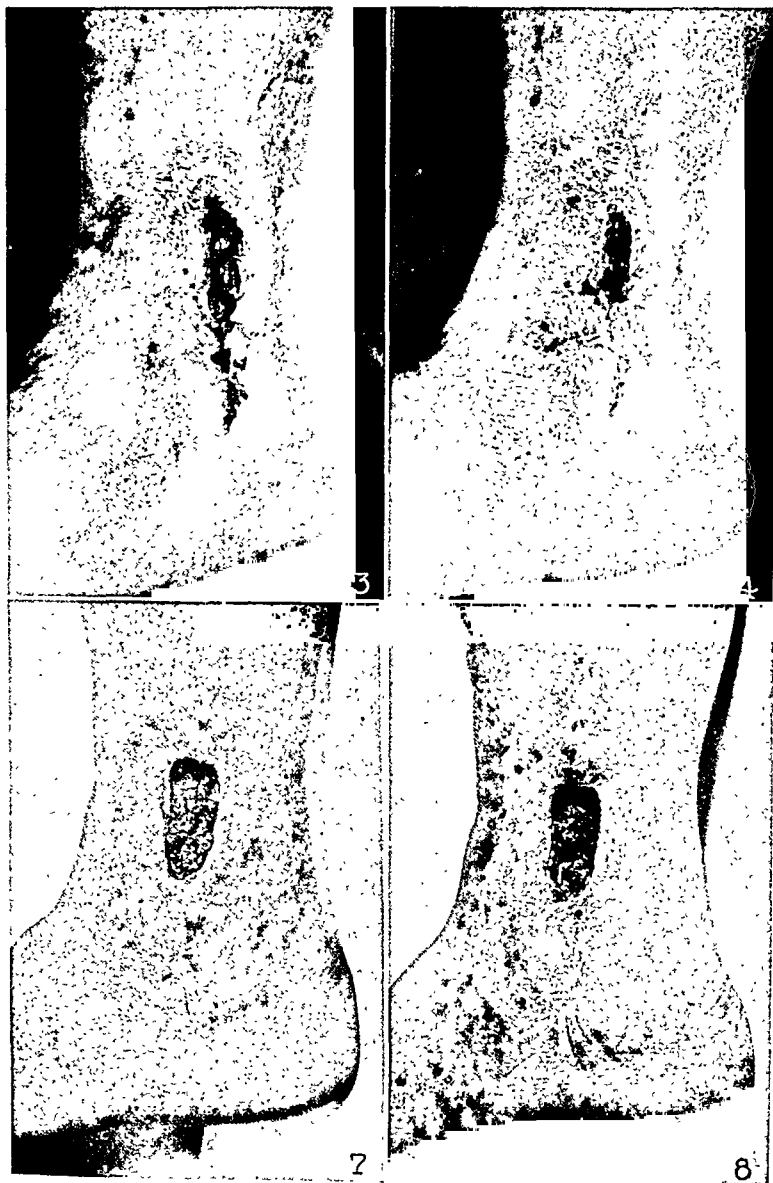


FIG. 2a.—*Thrombophlebitic ulcers* Case 11. The 8 photographs on this and the following page of a single extensive ulcer in a diabetic patient receiving insulin and acetyl- β -methylcholine chloride iontophoresis. Photograph 1 was taken on the first day of treatment, the others 1 month, 1 $\frac{1}{2}$, 2, 4, 13 $\frac{1}{2}$ (11 months after discontinuance of iontophoresis), 14 (after resuming iontophoresis), and 15 months later.

good. Ten of the patients had pain, 1 probably from arch strain, and 9 the typical aching and heavy feeling aggravated by being in the vertical position, and worse in the afternoon. Eight of these 9 were more comfortable shortly after starting treatment, 2 completely



relieved, 4 nearly so. Two of the patients had excessively painful menstruation since the onset of the phlebitis; 1 for 4 months, 1 for 5 years. Pelvic vein thrombosis was the probable cause. Both were promptly relieved of this symptom. Six of the patients had some

degree of edema of the lower leg: in none was the edema influenced by treatment. Careful measurements were made during the therapy of an asymptomatic, simple, milk leg (Case 33). The size was unchanged by treatment. After a month of bed rest, elevation and elastic bandage, the circumference was lessened from 1 to 2 cm. and the leg made softer.

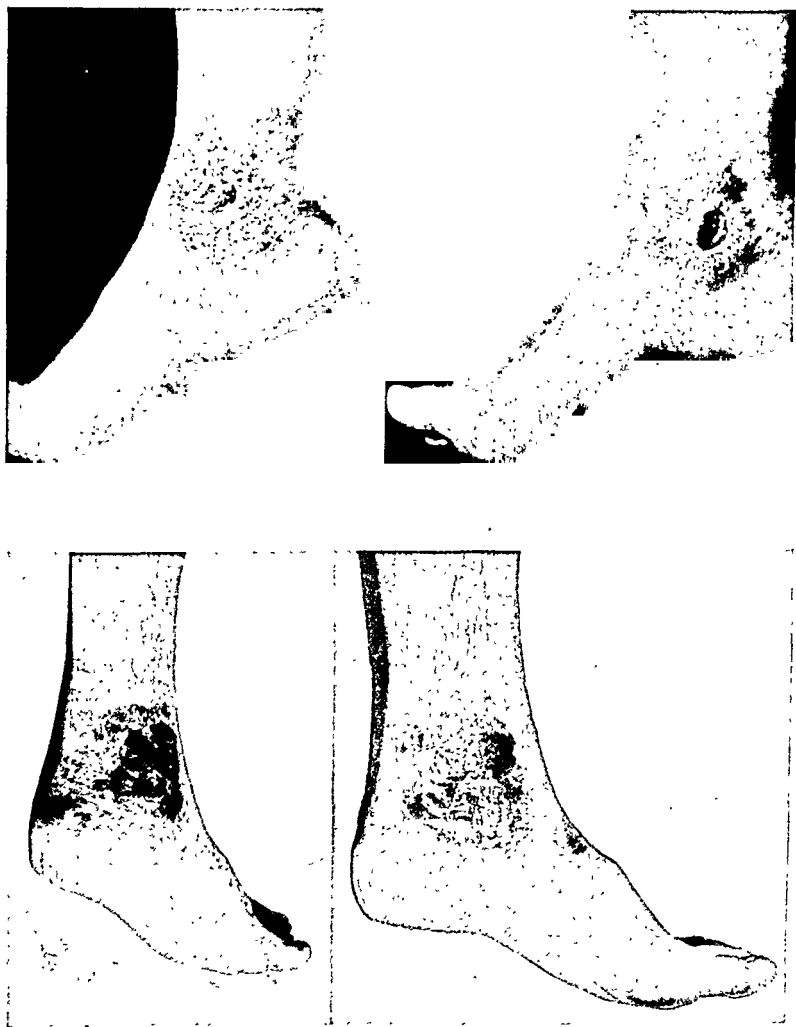


FIG. 2b.—*Thrombophlebitic ulcers.* Case 13. Two upper photographs: left view taken on first day of treatment, next one, right, 3 weeks later (worse). Case 14. Two lower photographs: left view taken on first day of iontophoresis, next 1 month later (improved).

These patients were followed too irregularly to secure a statistical appraisal of permanence of results. Two of the patients with heavy, tired feelings in the legs were relieved for 7 months, only to have the symptoms then return. In 1, prompt relief was again obtained



FIG. 3.—*Other ulcers.* Case 18, decubitus ulcer, upper two photographs: left taken on day first given iontophoresis, right taken 12 days later (healed). Case 21, ulcer, erythema induration, middle two photographs: left taken on day first given iontophoresis, right taken 1 month later (healed). Case 20, ulcer in amputation stump, lower two photographs: left taken on first day of iontophoresis, right taken 3 months later (healed).

after therapy. The other had developed varices for which high saphenous ligation was advised: she failed to comply. Improved footwear contributed to prolonged relief of 1 patient.

Scleroderma. Six patients with this disease were treated. In spite of prolonged therapy 1 continued to become worse, and 2 others were not measurably benefited (Fig. 4, Case 36). Two patients were moderately improved (Fig. 4, Case 35). One patient, with morphœa had a single thickened, hard, plaque of skin on the breast. This became almost normally soft within 2 weeks after starting therapy, and continued so with intermittent treatment for the 6 months in which the patient was followed.

Other Diseases. A patient with acrocyanosis and numb, stiff, blue hands, aggravated by cold, was entirely unimproved. A patient with brachial neuritis, which followed a thyroidectomy, obtained some temporary relief. One patient with fulminating Raynaud's disease with extreme pain and slight necrosis of finger tips was much improved either by iontophoresis or by cessation of smoking.

Untoward Effects. Undesirable effects of the drug were obtained in the case of 12 of the 42 patients. Atropine was needed only three times. The series of treatments of only 3 patients were discontinued (Cases 3, 10, 19). The single patient chosen for treatment with a history of asthma was at first able, and later unable, to tolerate 10 milliamperes for 10 minutes without having mild asthma precipitated (Case 3). Two patients with varicose ulcers each had two episodes of chills and fever, several hours after treatment, 1 to 103° (Cases 7, 10). The chills were probably caused by a transient bacteremia or toxemia resulting from greatly increased blood flow. One debilitated patient was barely able to tolerate 5 milliamperes for 10 minutes through a large decubitus ulcer (Case 19). Two patients who had no discomfort with 20 milliamperes for 20 minutes were later, at the 36th and 19th treatments, respectively, barely able to tolerate 5 milliamperes for 10 minutes because of severe local erythema (Cases 39, 41). One thrombophlebitic ulcer was painful when 10 milliamperes for 10 minutes was exceeded (Case 13). In another such patient temporary edema of the foot resulted, and in a third, superficial "flares" became excessively dilated in the skin area covered by the drug. Two patients complained, at several times during therapy, of a feeling of mild pressure under the sternum. No patient received a burn, against which precautions were taken, because when small electrodes were used they were used only with greatly reduced current, and because skin was constantly protected from metal of the electrodes.^{7,8}

Discussion. Judging from the experience of this clinic, the pharmacologic effects of acetyl- β -methylcholine chloride iontophoresis are as described by Kovacs.^{4a} There is consistently a great increase in blood flow, at least in the skin.^{4a,8} Undesirable side effects of the drug are mild if there is no history of asthma or of recent infec-



FIG. 4.—*Scleroderma*. Case 35, upper six photographs taken at three times, 1 and 1-a a week after starting iontophoresis, 2 and 2-a 10 months (improvement), and 3 and 3-a, 28 months after starting (slight relapse). Case 36, lower four photographs, left two taken at onset of iontophoresis, right pair taken 2 months later (slight improvement).

tion in the area of veins. The results of this therapy, however, were not as favorable as those previously reported. Longstanding, severe varicose ulcers were made less painful, cleaner, and smaller, but did not heal. The ulcers chosen were for the most part severe and this may explain the difference in results. Most of the other ulcers, post-thrombophlebitic, decubitus, and so forth, also failed to heal.

We believe that acetyl- β -methylcholine chloride iontophoresis should at times be used as an adjunct to the more usual forms of treatment of varicose and post-thrombophlebitic ulcers, but should be used only (1) after more direct methods such as supportive bandages and ligation of veins have failed, or (2) before the more severe forms of therapy such as prolonged bed rest or the Linton operation are undertaken. Its use preceding surgery lies mainly in the effect of cleaning ulcers: operative procedures can then be carried out with less danger of infection.

This clinic's experience in the treatment of scleroderma is much the same as that of Duryee and Wright.³ There is usually some prolonged softening of the skin, some subjective improvement, but little effect on the mobility of limited joints. Very prolonged therapy is necessary. Scleroderma also tends to respond to other simpler means of causing peripheral vasodilatation such as heat and thyroid medication. A favorable response to iontophoresis of the single patient with localized scleroderma (morphoea) suggests further trial (see Table 1).

The best results were obtained in the case of chronic thrombophlebitis without ulcer. Murphy⁹ has described a longer series. In most instances there was relief of afternoon discomfort. The effect is sufficiently prompt and of sufficient duration to recommend a trial of this therapy in these cases. The 2 instances in which dysmenorrhea was relieved by iontophoresis of the legs suggests a new occasional usefulness of the procedure. There are direct connections between the veins of the legs and the pelvic veins, and it is reasonable to suppose that blood carrying a relatively high concentration of the drug reaches the pelvic veins from the leg veins. Perhaps this causes dilatation of spastic pelvic vessels associated with other thrombosed pelvic vessels. There was no control in these cases using acetyl- β -methylcholine chloride by mouth. This should be done.

The cause of the beneficial clinical effect of acetyl- β -methylcholine chloride iontophoresis is unknown. The one pharmacologic effect which seems a reasonable cause for improvement of the diseases mentioned is the great increase in blood flow.^{4a,8} It is only fair to state that equal or greater increases in rate of blood flow can be obtained by local or reflex heat.⁸

Brief studies with Dr. James Forrester, on the effects of acetyl- β -methylcholine chloride iontophoresis on the growth of bacteria in agar, show no appreciable antibacterial action when the concentration of the drug and of the current are similar to those used thera-

apeutically. Saylor, Kovacs, Duryee, and Wright suggested that in addition to an increase in blood flow, diaphoresis may play a therapeutic rôle by relieving the tissues of an overload of fluid.¹⁰ The present observations fail to substantiate any reduction in edema. Acetylcholine plays a normal physiologic rôle² and it may be that acetyl- β -methylcholine, introduced in high concentration locally by iontophoresis, has some unknown parasympathicomimetic action which favors healing.

Summary. Acetyl- β -methylcholine chloride iontophoresis greatly increases cutaneous blood flow and is a useful adjunct to the therapy of some non-arterial peripheral vascular disorders. The augmented blood flow may be the cause of the improvement. It is recognized that the disorders for which the procedure has been recommended are chronic and usually relapsing under most forms of accepted therapy. There is some beneficial result in some cases of scleroderma, but therapy must be continued over a long period of time. Varicose and post-thrombophlebitic ulcers tend to become smaller, cleaner, and less uncomfortable, but they usually fail to heal and the benefits are usually transient. The procedure is recommended for the treatment of these ulcers only after more direct measures have failed or before surgical treatment is instituted. It is not a substitute for surgical measures designed to correct incompetence of venous valves, but it does help improve ulcers sufficiently to make surgery safer. The best results are obtained in relieving post-thrombophlebitic discomfort. The dangers of acetyl- β -methylcholine chloride iontophoresis are remote, with the exception of burns which occur when electrode metal touches skin, or when the importance of the relation of the strength of the current to the size of the electrodes is not appreciated.

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BOOK REVIEWS AND NOTICES

CONGENITAL SYPHILIS. By CHARLES C. DENNIE, B.S., M.D., Professor of Dermatology, University of Kansas Medical School, Kansas City, Kansas; Chief of the Department of Dermatology and Syphilology of Bell Memorial Hospital, Kansas City, Kansas, etc., and SIDNEY F. PAKULA, B.S., M.D., Visiting Pediatrician to Children's Mercy Hospital, Kansas City General Hospital, Alfred Benjamin Clinic and Menorah Hospital, Kansas City, Mo. Pp. 596; 133 illustrations. Philadelphia: Lea & Febiger, 1940. Price, \$8.00.

In a comprehensive work with ample bibliography and excellent illustrations, the authors take cognizance of a need in present-day medical literature for an adequate text, dealing with all phases of the management of congenital syphilis from the treatment of the pregnant syphilitic woman to prevent infection of the unborn child, to the management of the adult congenital syphilitic. The historical introduction stressing the problems in the detection and eradication of a disease which is usually symptomless in the expectant mother, and seldom clinically manifest in the newborn child during the neonatal period, gives much food for thought. The chapter on congenital syphilis of the bones and joints, and the one covering the eye changes in the congenital syphilitic (the latter by John McLeod and A. N. Lemoine) are especially well done. The authors have had the same difficulties in obtaining reproductions of roentgenograms of early congenital syphilis with sufficient bone detail to be understandable to any but the experienced, that characterizes almost all American and some European publications.

Throughout the work the authors have drawn upon a vast clinical experience and large and varied patient material. The discussions of the various aspects of the field are amply illustrated with case experience, in a manner however which might occasionally, for some individuals at least, detract from the clarity of the presentation. It is, for example, rather difficult, in spite of the considerable discussion about serologic and roentgenographic interpretation, for the reader to obtain a clear and concise impression of the procedure to be followed in making the diagnosis of infantile congenital syphilis, a seemingly important aspect of the subject. Likewise, the chapter on treatment commences with the statement, "A definite diagnosis of congenital syphilis having been established," when it would seem that a brief summary discussion orienting the reader in the indications for treatment might be in order.

The authors show a tendency to take definite stands on some controversial points in the congenital syphilis field. Among possibly criticizable statements are:

1. The suggestion that all offspring of adequately treated mothers would be better off with a year of active postnatal treatment for syphilis and that "in every instance the infants who are the issue of inadequately treated mothers should be treated no matter what the serologic reactions." This statement is also apparently meant to convey the impression that every child in a family discovered to contain one congenital syphilitic should be treated regardless of the individual physical or serologic status.

2. The recommendation that women with symptomatic late syphilis, particularly tabes (p. 92), and young mothers with early resistant syphilis (p. 103) be aborted.

The general discussion of the serologic diagnosis of syphilis in infancy

seems considerably weakened by: 1, The failure of the authors to make direct mention of the quantitative titrated Wassermann studies and conclusions of such authors as Faber and Black, Christie and J. A. V. Davies; 2, the apparent stress placed upon serologic diagnosis by multiplicity of positives (or negatives) in various antigens on the same specimen of blood rather than upon repeat specimens; and, 3, such statements as that a quantitative serologic reaction should be done on patients in whom the specific reagins are present in such small amounts that a qualitative reaction does not pick them up. This last is, of course, a matter of sensitivity of the test rather than of titration. The fact that the authors apparently consider the positive blood serologic test on the newborn child to be of absolute diagnostic import at the age of 3 weeks (p. 84), at the age of 2 weeks (p. 86), and at the age of 6 weeks (p. 88) is also a little confusing.

The authors' advice, on the other hand, against the use of mercury rubs in active infantile congenital syphilis and against the continuous energetic treatment over a period of years of the seroresistant asymptomatic late congenital syphilitic seem to conform to the best current viewpoints and are especially worthy of stress.

N. I., Jr.

THE VASOMOTOR SYSTEM IN ANOXIA AND ASPHYXIA. A Study of the Adjustment Reactions of the Mammalian Organism (Illinois Medical and Dental Monographs, Vol. II, No. 3). By ERNST GELLHORN, M.D., PH.D., Professor of Physiology, and EDWARD H. LAMBERT, M.D. Pp. 71; 21 illustrations. Urbana, Ill.: The University of Illinois Press, 1939. Price, \$1.00.

THE authors of this monograph review the literature and include an excellent bibliography. They make a study, as measured by changes in blood pressure, of the effects of anoxia, excess carbon dioxide, and a combination of the two, on the vasomotor center of anesthetized artificially ventilated dogs. The major conclusion to be drawn from this work is that anoxia augments the response of the vasomotor center to carbon dioxide in the intact animal. Since this augmentation is also present after denervation of the carotid and aortic bodies it is due in part to direct stimulation of the vasomotor center by anoxia. The contribution would have been of more value if the authors had included blood gas studies and more data as to the constancy of these phenomena.

P. D.

DEVELOPMENTAL ANATOMY. A Text-book and Laboratory Manual of Embryology. By LESLIE BRAINERD AREY, PH.D., Sc.D., LL.D., Robert Laughlin Rea Professor of Anatomy, Northwestern University. Pp. 612; 590 illustrations, some in color. Fourth Edition, revised. Philadelphia: W. B. Saunders Company, 1940. Price, \$6.75.

THE author's *Developmental Anatomy* was written for medical students and since the appearance of the first edition it has been one of the favorite texts of students interested primarily in human embryology. The fourth edition not only carries on the tradition of the earlier ones, but its structure is even more substantial. Numerous figures have been added, some diagrammatic in nature, illustrating various phases or processes of development. Others give three-dimensional aspects of certain regions of the embryo. In addition, microphotographs have been included, giving valuable information to the student on early phases of development which cannot be studied in the laboratory. Although it contains numerous illustrations, the book is not overcrowded with pictures. A proper balance

has been preserved between text and figures. The text is as simple and clear as in the earlier editions; the changes are not corrections, but additions. The author has brought the material up to date, including all important discoveries in mammalian embryology reported since the publication of the third edition. Undoubtedly the book will be received by student and teacher with equal enthusiasm, for the reader realizes the serious effort involved in the preparation of such a volume. Only a sincere scientist, a good teacher and an expert publisher could produce such a fine book for medical students.

G. de R.

A REVIEW OF THE PSYCHONEUROSES AT STOCKBRIDGE. A Case Study and Statistical Analysis. By GAYLORD P. COON, M.S., M.D., Chief Medical Officer, Boston Psychopathic Hospital, and ALICE F. RAYMOND, A.B., Statistician, Department of Child Hygiene, Harvard School of Public Health. Pp. 299; 2 figures and 66 tables. Stockbridge, Mass.: Austen Riggs Foundation, Inc., 1940.

THIS study is of the histories of patients treated during the years 1910-1934 and an evaluation of the therapeutic results. In the Berkshires, near the center of the old New England village of Stockbridge, are two houses with the outward appearance of quiet country inns. Within are quartered some 50 patients, unrestrained by barred windows or locked doors, and cared for by ununiformed nurses. Such "guests" as are able to be about partake of the town life as do the residents. Nearby are the doctors' offices, where others who are able visit their physician each day. There is an occupational therapy shop, indoor and outdoor games and sports, presided over by a recreational director. A group of 1060 patients—approximately 20% of those admitted—were studied and the diagnoses were almost invariably neurasthenia or anxiety neurosis. It is believed a marked imbalance of the instinctive drives and a high degree of hypersensitivity, are the main predisposing factors. The therapeutic approach is reeducation and is akin to the "persuasion" technique of Dubois together with the "psychobiological" concepts of Adolph Meyer.

N. Y.

PROGRESS IN MEDICINE. A Critical Review of the Last Hundred Years. By IAGO GALDSTON, M.D. With a Foreword by HENRY E. SIGERIST, M.D. Pp. 362. New York: Alfred A. Knopf, 1940. Price, \$5.00.

NEITHER a conventional history of the medicine of the past century nor a digest of recent medical progress, this thoughtful work sketches with broad strokes the main medical trends of this prolific period. Ideas rather than heroes are stressed, though with the author's skillful handling sufficient personal touches are introduced to give some revealing pictures of the leading personalities as they appear. Microbes first hold the stage for 4 chapters, then a chapter on nutrition—but stressing the vitamins—another on the endocrines and the *milieu intérieur*, 2 on psychiatry, then "a century of clinical progress," illustrating some of the triumphs of diagnosis, preventive medicine and recent therapeutic successes. In a final chapter on "Whither Medicine" the author gives us some interesting views on what he calls personal preventive medicine, *i. e.*, "the development and realization of the individual's potentialities for growth, achievement and well being." Here he finds there is still plenty of room for improvement. We not only welcome this mature presentation as a source of entertainment, but also believe that it may help the reader to a better understanding of modern medical progress than he would perhaps get from a larger more detailed work.

E. K.

THE CHRONICLE OF CRICHTON ROYAL (1833-1936). Being the Story of a Famous Mental Hospital During Its First Century, and Illustrating the Evolution of the Hospital Care and Treatment of Mental Invalids in Scotland. By CHARLES CROMHALL EASTERBROOK, M.A., M.D., F.R.C.P.E., Physician Superintendent, 1908-1937, and the late SIR JAMES CRICHTON-BROWNE, M.D., LL.D., F.R.S. Pp. 663; 103 illustrations and map. Dumfries, Scotland: Courier Press, 1940. Price, 25/.

BEGINNING about a century ago with the lavish endowment of 100,000 pounds, Crichton Royal has always maintained the highest possible standard of its care and treatment of those mentally afflicted. This chronicle gives the intimate details of that famous Scottish institution, which, as stated, will be of most interest to those who have been, are now, and shall be associated with the institution. N. Y.

THE HISTAMINE AND INSULIN TREATMENT OF SCHIZOPHRENIA AND OTHER MENTAL DISEASES. By HORACE HILL, M.R.C.P., Medical Superintendent, Laverstock House Mental Home, Salisbury, England. Pp. 133. Baltimore: The Williams & Wilkins Company, 1940. Price, \$1.75.

IN this author's investigations, treatment was begun with insulin, then histamine alone was used, and finally their use was combined. Stating that histamine is found in all varieties of shock, he believes it is histamine and not shock that gives the favorable results. The method is described as having led to improvement in hitherto unimproved patients. Symptoms were lessened or entirely overcome in some severe and long-standing schizophrenic patients. Good results were also obtained in "other cases as manic-depressive melancholia, paranoiac conditions and especially in stupor." In old patients with thick and rigid arteries, the method is useless. When employed by competent physicians, the régime is not dangerous and not unpleasant. There are many brief case reports. The text is rather loosely written and there is the frequent misuse of the word "case" for "patient"—"case got well," "case was not mine;" and, "case H's husband." N. Y.

THE FUNDAMENTALS OF NUTRITION. By ESTELLE E. HAWLEY, PH.D., and ESTHER E. MAURER-MAST, M.D., University of Rochester, School of Medicine and Dentistry, Rochester, New York. Including Table of 100-Calorie Portions, by ESTELLE E. HAWLEY, ESTHER E. MAURER and HERBERT F. VAN EPPS, The Department of Vital Economics, University of Rochester and discussions of the Dietary Management in Specific Conditions, by Collaborators associated or formerly associated with The University of Rochester, School of Medicine and Dentistry. With a Foreword by JOHN R. MURLIN, PH.D., Sc.D., Professor of Physiology and Director of the Department of Vital Economics, University of Rochester. Pp. 477; illustrated. Springfield, Ill.: Charles C Thomas, 1940. Price, \$5.00.

THIS book reports the experience gained in the Department of Vital Economics in the University of Rochester, particularly as regards the extensive instruction in nutrition now carried on in that school. The monograph presents both the fundamentals for the normal and a discussion of the diet management of specific conditions by 19 collaborators associated with the School of Medicine and Dentistry of the University. The text is ideal as a teaching manual.

The book is divided into five sections. The first deals with the fundamentals of metabolism and summarizes the energy requirements of the body. The second section considers the fundamentals of nutrition, classification

of foods, nature of the nutrient elements, normal diet and composition of low cost meals.

The third section covers diseases of metabolism, of the digestive tract and specific disease groups such as anemias, cardiovascular, food allergy and toxemia of pregnancy. There is an excellent section on the treatment of surgical patients, and one on vitamin deficiencies.

The fourth section, on the planning of diets, is based for simplicity upon the method of 100-calorie portions. The authors feel that the 100-calorie portion establishes a common basis for comparison and is easily visualized, since it is so frequently used as an "average serving" or is a simple multiple of it. In this section on diet planning there are numerous illustrations to explain the choosing of foods to make up the necessary equivalents of various elements.

In the appendix (Section 5) there is an excellent outline for the research worker in the evaluation of nutritional statistics. Special chapters on the study of milk, an analysis of commercial vitamin products, allergies and infections follow, and there are three chapters on diet instruction of patients, miscellaneous items and food suggestions for special conditions.

This volume not only is a good textbook for the medical student or nutritionists, but should also be regarded as a reference volume by research workers, dietitians and practising physicians.

P. W.

INTRODUCTION TO MEDICINE. By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University School of Medicine; Attending Physician, Medical Division of the Cook County Hospital, etc. With Introduction by ADA BELLE McCLEERY, R.N., Superintendent, Evanston Hospital, Evanston, Ill. Pp. 642; 144 illustrations and 14 color plates. St. Louis: The C. V. Mosby Company, 1940. Price, \$3.25.

As a textbook for the beginning student nurse this book would not be suitable. The author attempts to cover too many subjects and consequently is entirely too brief to be accurate. For instance in the chapter on the "Functional Nervous Disorders" he covers "Hysterical Fits" in three lines. It is a mistake for any one to believe that one textbook could adequately cover the variety of subjects included in this book. As a reference book the illustrations would be very useful.

M. S.

A TREATISE ON MEDICO-LEGAL OPHTHALMOLOGY. By ALBERT C. SNELL, M.D., Lecturer in Ophthalmology, School of Medicine and Dentistry, University of Rochester; Consultant in Ophthalmology, Strong Memorial and Rochester General Hospitals, etc. Pp. 312; illustrated. St. Louis: The C. V. Mosby Company, 1940.

COMPENSATION of industrial accidents makes it necessary for the examining physician to give expert opinion concerning eye injuries to non-medical groups. This is also true of eye injuries arising as a result of the increasing number of motor accidents.

It is important therefore for all ophthalmologists to know the essential rules of evidence, forms of legal procedure, and his own rights and obligations as a medical witness. This book sets forth these problems in medical jurisprudence and should be extremely valuable for all who practice ophthalmology.

In addition, the author has set forth the result of his years of study and research on the evaluation of functional loss of the eye. He presents a method by means of which the loss of useful visual function can be presented accurately on a percentage basis.

F. A.

ROSE AND CARLESS MANUAL OF SURGERY. American (Sixteenth) Edition, edited by WILLIAM T. COUGHLIN, B.S., M.D., F.A.C.S., Professor of Surgery and Director of the Department of Surgery, St. Louis University School of Medicine; Surgeon-in-Chief, St. Mary's Group of Hospitals, St. Louis. From the Sixteenth English Edition by CECIL P. G. WAKELEY, D.Sc., F.R.C.S., F.R.S.E., F.R.S.A., F.A.C.S., F.R.A.C.S., Fellow of King's College, London; Senior Surgeon, King's College Hospital; Temporary Surgeon-Rear-Admiral, etc., and JOHN B. HUNTER, M.C., M.CHIR. (CANTAB.), F.R.C.S. (ENG.), Surgeon, King's College Hospital, etc. Pp. 1656; 1034 illustrations and 30 plates (some in color). Baltimore: The Williams & Wilkins Company, 1940. Price, \$9.00.

THE fact that this is the sixteenth American edition is evidence of the continuing popularity of this "manual." Manual is hardly an appropriate term since it has become expanded to the full dimensions of a textbook over the years.

While it has been kept fairly up to date in methods or treatment, it lacks the physiologic approach to the problems of surgery that several of the modern American textbooks now have. This is a volume which will, at least in this country, be used more frequently by surgeons than by medical students, for it is now too large to be used for third and fourth year students.

I. R.

FEEDING THE FAMILY. By MARY SWARTZ ROSE, PH.D., Professor of Nutrition, Teachers' College, Columbia University. Pp. 421; illustrated. Fourth Edition. New York: The Macmillan Company, 1940. Price, \$3.75.

IN this well-known volume, the author has recognized the advances in the solution of dietary problems in recent years, particularly in regard to allergy, which now forms the new chapter. Of particular importance to the head of the family, for whom this book is intended, are chapters on the cost of food, making the menus, and food for the family group. The author discusses the requirements of the various food factors for the different ages in a separate chapter. There are 6 chapters devoted to various diets for children from infancy to adolescence, and the requirements for adults and senile individuals are also portrayed. In the various diets which have been presented in different classes, he has specified not only the fuel values and cost but weight and protein caloric value as well, and in such a manner that they should be easily understood by persons of average intelligence. There is a well-developed chapter on food for the sick and convalescent. An appendix on nutritive values of foods and diet recipes contain much practical information. This book is highly recommended to the laity.

P. W.

SURGERY OF THE HAND. By R. M. HANDFIELD-JONES, M.C., M.S., F.R.C.S., Surgeon to Outpatients, St. Mary's Hospital; Senior Surgeon, Florence Nightingale Hospital, etc. Pp. 140; 95 illustrations (several in color). Baltimore: The Williams & Wilkins Company, 1940. Price, \$4.50.

THIS short monograph makes no attempt to take the place of the classic monograph on the surgery of the hand by the late Allen B. Kanavel. It is in fact dedicated to him. It stresses the improvements in treatment in this field in a splendid manner. The paper and format are excellent. The illustrations are as fine as any the Reviewer has seen. Although the discussion is brief it is adequate. Here is a monograph that every intern, general practitioner and surgeon can own with pride.

I. R.

A SURGEON'S LIFE. The Autobiography of J. M. T. FINNEY. Pp. 396; 1 illustration. New York: G. P. Putnam's Sons, 1940. Price, \$3.50.

IN this increasingly industrial and mechanical age we often ponder the question as to whether one of the many things that have been sacrificed may be the development of the rich and colorful personalities that were not uncommon in the past but seem so rare as we look about us. Perhaps it is the experience of each generation to feel so about contemporaries, but as one reads the author's account of "A Surgeon's Life" and is aware of the mellow, full character that emerges from its pages, one wonders whether the present and future will permit this personal development.

The author has lived in a period of great strides in the development of surgery and he was associated with one of the great leaders in this development, William Stewart Halsted. This autobiography makes the "great four" of Johns Hopkins Medical School, Osler, Halsted, Welch and Kelly, live again. The vividly told anecdotes of these men and their associates are a real contribution.

The author has well pointed out that emphasis on the science of surgery to the exclusion of the art of surgery may be fraught with grave danger. No one could realize this better than the author, whose knowledge of the human side of medicine is unsurpassed by any living surgeon.

The author reveals his character on every page of this book—his kindly humor, his appreciation of the humor of others, his tempered judgment, all of the characteristics that are known and appreciated by every younger surgeon who had had the privilege of contact with him. I. R.

THE NEUROSES IN WAR. By several authors under the editorship of EMANUEL MILLER, M.D. (CANTAB.), M.R.C.P., D.P.M. (CAMB.), with a concluding chapter by H. CRICHTON-MILLER, M.D., F.R.C.P. Pp. 250. New York: The Macmillan Company, 1940. Price, \$2.50.

THIS book is the collaborated work of 11 neuropsychiatrists and an anonymous contributor, who "believe there is a very high degree of agreement over subjects which still remain somewhat controversial." If this be true, it is an achievement. The subject matter is discussed in 11 chapters and an appendix, as follows: A Survey of the Literature of Neuroses in War; Mode of Onset of Neuroses in War; Clinical Case Studies and Their Relationships; Differential Diagnosis of the Psychoneuroses of War; Psychopathological Theories of Neuroses in Wartime; Treatment of Neuroses in the Field; The Advanced Psychiatric Center; Treatment by Suggestion and Hypo-analysis; Technique of Other Psychotherapeutic Methods; Psychiatric Organization in the Services; The "War of Nerves," Civilian Reaction, Morale and Prophylaxis; General Conclusion; Appendix A: Extracts From the "Report of the War Office Committee of Enquiry on Shell Shock" (1922). B: Description of the Treatment Facilities for Civilian Psychoneurotic Casualties Provided by the Emergency Medical Service (1940). C: Classification of Psychological Disorders in War. D: Psychiatric Pharmacology.

War neuroses may be treated by suggestion, reëducation, persuasion and by hypnoanalysis. In hypnoanalysis the effort is to release repressed fears through hypnosis, and to have the patient re-live his traumatic experiences; then, through suggestion, the necessary adjustment follows. Psychiatric pharmacology is an important section. It includes the method for narco-analysis through the use of evipan-sodium; by thus overcoming resistance, emotions repressed at the time of the trauma because of some restraining influence, may then through suggestion be brought into the field of full consciousness. The method is not without danger and should only be employed by experienced physicians. Psychoanalysis in the Freudian sense is not recommended. The survey of literature is excellent, the bibliography is pertinent but the index is brief. N. Y.

NEW BOOKS.

Bacillary and Rickettsial Infections. Acute and Chronic. A Textbook. Black Death to White Plague. By WILLIAM H. HOLMES, Professor of Medicine, Northwestern University Medical School, etc. Pp. 676. New York: The Macmillan Company, 1940. Price, \$6.00.

Foreign Bodies Left in the Abdomen. The Surgical Problems, Cases, Treatment, Prevention. The Legal Problems, Cases, Decisions, Responsibilities. By HARRY STURGEON CROSSEN, M.D., School of Medicine, Washington University, and DAVID FREDERIC CROSSEN, LL.B., School of Law, Washington University, St. Louis. Pp. 762; 212 illustrations, including 4 color plates. St. Louis: The C. V. Mosby Company, 1940. Price, \$10.00.

The Doctor and the Difficult Child. By WILLIAM MOODIE, M.D., F.R.C.P., D.P.M., Medical Director, London Child Guidance, Clinic and Training Centre. Pp. 214. New York: The Commonwealth Fund, 1940. Price, \$1.50.

Psychotherapy. Treatment That Attempts to Improve the Condition of a Human Being by Means of Influences That Are Brought to Bear Upon His Mind. By LEWELLYS F. BARKER, M.D., Emeritus Professor of Medicine, Johns Hopkins University; Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 218. New York: D. Appleton-Century Company, Inc., 1940. Price, \$2.00.

The Diagnosis and Treatment of Diseases of the Heart. By HENRY A. CHRISTIAN, M.D., Sc.D. (Hon.), LL.D., F.A.C.P., Hon. F.R.C.P. (Can.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University; Physician-in-Chief, Emeritus, Peter Bent Brigham Hospital, Boston. (Reprinted from Oxford Monographs on Diagnosis and Treatment.) Pp. 599; 28 figures. New York: Oxford University Press, 1940.

The Endocrine Function of Iodine. By WILLIAM THOMAS SALTER, Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Thorndike Memorial Laboratory, Boston City Hospital. Pp. 351; 40 figures and 45 tables. Cambridge, Mass.: Harvard University Press, 1940. Price, \$3.50.

From Thirty Years With Freud. By THEODOR REIK. Translated by RICHARD WINSTON. Pp. 241. New York: Farrar & Rinehart, Inc., 1940. Price, \$2.50.

Diagnosis and Treatment of Menstrual Disorders and Sterility. By CHARLES MAZER, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to the Mount Sinai Hospital, Philadelphia, and S. LEON ISRAEL, M.D., F.A.C.S., Instructor in Gynecology and Obstetrics, School of Medicine, University of Pennsylvania; Associate Gynecologist to the Mount Sinai Hospital, Philadelphia. Pp. 485; 88 illustrations and 1 colored plate. New York: Paul B. Hoeber, Inc., 1941. Price, \$6.50.

Medical Index of Hospital Equipment, Medical Supplies, Surgical Instruments and Orthopedic Appliances, Volume 1, No. 1, December, 1940. Pp. 13; illustrated. New York: Medical Index, Inc., 1940. Price, 25c single copy; \$2.00 per year.

Offered as "the only publication in the profession field, devoted exclusively to the tools of medical practice and surgery."

Diagnosis and Treatment of Arthritis and Allied Disorders. By H. M. MARGOLIS, M.D., M.S. (in med.), F.A.C.P., Chief, Arthritis Service, St. Margaret Memorial Hospital; Associate in Medicine, Montefiore Hospital; Consultant in Medicine, Pittsburgh Diagnostic Clinic. Pp. 551; 140 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, \$7.50.

Clinical Pellagra. By SEALE HARRIS, M.D., Professor Emeritus of Medicine, University of Alabama, Birmingham, assisted by SEALE HARRIS, JR., M.D., Formerly Assistant Professor of Medicine, Vanderbilt University, Birmingham, Ala. With a Foreword by E. V. McCOLLUM, PH.D., Sc.D., LL.D., Professor of Biochemistry, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore. Pp. 494; 66 illustrations and 16 tables. St. Louis: The C. V. Mosby Company, 1941. Price, \$7.00.

Physiology of the Fetus. Origin and Extent of Function in Prenatal Life. By WILLIAM FREDERICK WINDLE, Professor of Microscopic Anatomy, Northwestern University Medical School. Pp. 249; 70 illustrations and 27 tables. Philadelphia: W. B. Saunders Company, 1940. Price, \$4.50.

Doctrina y Practica de la Profilaxis de la Tuberculosis. By LUIS SAYÉ, Profesor de la Universidad de Barcelona; Director del Servicio de Examen de Colectividades del Ministerio de Salud Pública del Uruguay. Pp. 355; 170 illustrations. Buenos Aires: Editorial Sudamericana, S. A., n.d.

The four sections of this work are devoted to: 1, epidemiologic investigations; 2, the technique and results of B.C.G. vaccination; 3, Abreu's method of radio-photography in the diagnosis of tuberculosis; 4, prophylaxis of tuberculosis.

Bacteriology in Neuropsychiatry. A Survey of Investigations Concerned With the Specified Role of Infectious and Immune Processes. By NICHOLAS KOPELOFF, PH.D., Research Bacteriologist, New York State Psychiatric Institute and Hospital, New York. Pp. 316. Springfield, Ill.: Charles C Thomas, 1941. Price, \$4.50.

A Textbook of Clinical Neurology. By J. M. NIELSEN, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine (Neurology), University of Southern California; Senior Attending Physician (Neurology), Los Angeles County General Hospital; Attending Neurologist, Hospital of the Good Samaritan, Los Angeles. Pp. 672; 179 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, \$6.50.

The Medical Reports of John Y. Bassett, M.D. The Alabama Student. With an Introduction by DANIEL C. ELKIN, M.D., Joseph B. Whitehead Professor of Surgery, Emory University. Pp. 62; illustrated. Springfield, Ill.: Charles C Thomas, 1941. Price, \$1.50.

NEW EDITIONS.

Methods of Treatment. By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals, and EDWARD H. HASHINGER, A.B., M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals, and St. Luke's Hospital, Kansas City, Mo. With Chapters on Special Subjects by 12 Contributors. Pp. 997; 138 illustrations. Seventh Edition. St. Louis: The C. V. Mosby Company, 1941. Price, \$10.00.

The Merck Manual of Therapeutics and Materia Medica. A Source of Ready Reference for the Physician. Pp. 1436. Seventh Edition. Rahway, N. J.: Merck & Co., Inc., 1940. Price, \$2.00.

This convenient compend is now brought down to date by the inclusion of 12 new chapters and of new remedies such as the sulfonamide derivatives, suprarenal cortex, nicotinic acid, and numerous others that have become available since the last edition was published (1934). It seems quite adequate and authoritative and should be very useful for the purpose for which it was intended, viz. to make available in compact form the bare essentials of diagnosis and treatment of important diseases.

C. S.

PROGRESS OF MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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HEPARIN.

IN 1916, McLean,¹⁰ while working on cephalin in Howell's laboratory, reported isolating an active anticoagulant from liver tissue. Howell^{6a} studied this substance, giving it the name "heparin," and concluded that it was probably a glycuronic acid derivative. For some time heparin was used in laboratory experiments as an anticoagulant but it was found to be toxic when given in any quantity to animals. Mason,¹¹ Howell,^{6b} and Godlowski⁴ have reported the use of heparin in transfusions. Mason found toxic reactions in about half of his patients, though with the more highly purified heparin less of the substance was needed and reactions were fewer. Howell used a fairly potent preparation. Godlowski, using small amounts of heparin, found no evidence of toxicity.

In 1933, Charles and Scott³ and Schmitz and Fischer¹⁴ published their studies on the analysis and preparation of purified heparin. The method devised by Charles and Scott made it possible for the Connaught Laboratories to produce a purified crystalline barium salt with a potency of about 500 Howell units per milligram, or 100 units according to their own standardization. For some time heparin for clinical use has been made in Canada, Sweden and Switzerland. The price, however, was so high that the general clinical use of heparin was impractical. It has since been made by the Connaught Laboratories at a price which permits its wider use when indicated. Within the past few months it has been made by an American firm and soon will be made by several other companies.

A review of the history and chemistry of heparin with a full bibliography to that date can be found in the article of Morton F. Mason.¹² It would be repetitious to reprint it here, so we shall confine ourselves to the present clinical uses of heparin.

Administration. Purified heparin can be administered locally, subcutaneously or intravenously. It is unfortunate that there is no agreement on the standardization of this substance so that amounts in units

cannot be given without specifying the particular preparation. Best¹ says "A unit has never been defined exactly. It is usually stated to be the amount of anticoagulant which inhibits for 24 hours the clotting of 1 cc. of blood under certain conditions of temperature and so forth. We have suggested as a provisional unit the activity contained in 0.01 mg. (10 γ) of the barium-free material, that is, 100 units per mg. This would make a convenient unit from both the physiological and the clinical aspect." This unit is accepted for the preparation of the Connaught Laboratories, but the units of the Swedish and Swiss preparations are not the same. The Best unit is equal to about 5 of the Howell cat units.

The dosage will vary according to the response of the patient but as a rule 20 to 30 units (Best) per kg. per hour will keep the clotting time at about a 20- to 30-minute level. The dose should be controlled by repeated estimations of the clotting time of the patient's blood. We have found the Lee-White method very satisfactory for determining the coagulation time.

In connection with the dosage and administration of heparin, it is well to keep in mind the fact that protamine has an antagonistic effect and will quickly neutralize the anticoagulant effect of heparin. If, after heparinization, a hemorrhage should start, or an immediate operation should become necessary, the normal clotting time of the blood can be rapidly restored by the administration of protamine. Jaques, Charles and Best⁷ say "There appears to be a direct proportionality between protamine and heparin, 1 mg. of protamine neutralizing 0.3 mg. of heparin. The heparin effect is annulled if the heparin is injected within approximately 1 hour after the protamine. On the other hand, if the anticoagulant is administered more than an hour after protamine the neutralizing effect of the latter is not observed."

The local use of heparin, incorporated in vaseline, in the suture of vessels has not had any success. Regional heparinization has been of value in experimental work and may well be of some clinical value. Small amounts of heparin are injected proximal to the site of vessel suture, so that the clotting time of the blood is increased before it reaches the operative field. If the amount used is small the clotting time of the blood in other limbs or areas will not be affected.

Heparin may be administered subcutaneously but larger doses are required and the level of clotting time cannot be controlled satisfactorily. The most effective and best controlled method of administration is by continuous intravenous infusion, the amount being governed by repeated determinations of the clotting time of the blood.

When a single dose of heparin is given intravenously there is a rapid but transitory effect on the clotting time. In order to obtain an effect for as much as an hour a relatively large dose of heparin is required, the clotting time is high immediately after the injection, returning to normal somewhat abruptly after an hour or so.

When heparin is given continuously the desired level of clotting time can be maintained for as long as necessary, that is, over a period of days or even weeks. An initial injection to establish a high level may be desirable, the level being maintained by the continuous intravenous infusion.

Indications for the Clinical Use of Heparin. While heparin has been used in the experimental laboratory for some years for a variety of studies, its clinical value is just beginning to be appreciated, and it is quite possible many more indications for its use will develop.

Our own experience with heparin has been in the removal of emboli by arteriotomy and in the treatment of thrombosis and embolus in general. One of us (I. S. R.) had the opportunity of demonstrating the value of heparin following the removal of a saddle embolus from the bifurcation of the aorta, which occurred 14 days after a coronary occlusion in a man of 32. Heparin was given continuously for 13 days. It is now 2 years since the operation and the patient is actively at work, with normal lower extremities. Since "the chief handicap to this form of treatment and one which provides the strongest argument for those in favor of the conservative treatment, is that not infrequently the site at which the embolus is lodged, as well as the point at which the vessel is opened, becomes thrombosed again," it is evident that heparin is "an agent which would entirely change the prospects of" an operation of this type "by keeping the lumen of the vessel patent after the embolus was removed."^{13b} Murray,^{13a} in 1936, reported 12 successful arterial embolectomies in which heparin was used.

Following the lodgment of an embolus there occurs marked vascular contraction distal to the embolus and within a short time a thrombus begins to form on the embolus. The thrombus extends most rapidly in the proximal direction. Thus, two factors operate further to reduce the rate of blood flow to the affected part. If vascular contraction can be relieved in part by intravenously injected papaverine or by paravertebral sympathetic injection, and the heparin prevent the extension of the thrombus many extremities can be saved even without surgery. The same principles undoubtedly apply to other anatomic areas such as the abdomen and chest. It is upon this basis that much of our therapy has been conducted.

Encouraging results have followed the use of heparin in the conservative treatment of mesenteric thrombosis, pulmonary embolism and thrombosis in the extremities. One of us (I. S. R.) has treated 2 cases of mesenteric thrombosis, both of whom recovered without resection even though there were clinical signs of massive involvement of the gut. Murray^{13a} has reported that "in the opinion of many surgeons, and from the literature on the subject the mortality rate in this disease is between 85 and 95 per cent. Most surgeons have never seen a case requiring resection of the bowel recover. In the face of these odds, it probably is a significant fact that the first 4 cases recovered without complications and are still alive and well. The next 2 cases had no further gangrene of bowel and died of other complications. Of all the clinical tests to which heparin has been put, this one is probably the most severe, and one is glad to report that the results have been most satisfactory." Thrombosis of the central vein of the retina has been treated successfully with heparin,^{2,5} the heparin possibly preventing extension of the process, and furthering resorption of the hemorrhage.

It is difficult to evaluate the results of heparinization in pulmonary embolus for recovery follows a varying percentage of these accidents. We have seen several patients with clinical evidence of a massive embolus recover, however, following heparinization.

Whipple¹⁵ and Murray^{13b} have reported that the postoperative use of heparin will prevent the portal thrombosis which occasionally is observed following splenectomy for Banti's syndrome or familial jaundice.

The use of heparin in coronary thrombosis has been very limited. It is likely that heparin, if used early, would prevent the extension of the thrombosis in the coronary vessels and in addition prevent a thrombus upon the endocardium adjacent to the infarcted area. If this can be accomplished it will reduce greatly the incidence of secondary emboli and the extent of the infarction, and as a consequence reduce the mortality of the lesion.

A promising extension of the use of heparin is suggested by Lehman and Boys^{8a,b} in their reports on "The Prevention of Peritoneal Adhesions With Heparin." Using rabbits they studied the formation of adhesions following mechanical trauma and bacterial contamination. After both mechanical trauma and bacterial contamination all the rabbits in each group developed adhesions. When heparin in salt solution was introduced into the peritoneal cavity, one rabbit (1%) of the traumatized group and none of the contaminated group developed adhesions. In the dog, adhesions were induced by bacterial contamination and then divided. "In all the control dogs a greater number of adhesions reformed than were divided" (157% average). "The heparin-treated animals presented only 25 per cent of the number of the original adhesions. The numerical difference is less striking than the observed difference at celiotomy. In the control animals, the reformed adhesions were largely extensive bands or sheets of adherence. In the heparin animals, the reformed adhesions were uniformly minute points of attachment, largely of omentum to the knots of silk ligatures." The further studies of this aspect of heparin treatment will be followed with interest.

The treatment of infected thrombi with heparin and chemotherapy is just now developing. The report of Lyons⁹ of 2 patients with bacteriemic staphylococcal cavernous sinus thrombophlebitis is encouraging for this condition is, as a rule, fatal. Whether further treatment of endocarditis with heparin and chemotherapy will bear out some of the earlier favorable reports is still a question.

The whole field of heparin therapy offers a challenge, for undoubtedly as we become more familiar with this substance, new uses for it will become evident.

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OPHTHALMOLOGY.

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RIBOFLAVIN AND KERATITIS.

ALTHOUGH several experimental workers had called attention previously to the occurrence of inflammatory conditions of the eyes and eyelids in young albino rats kept on a diet deficient in riboflavin, the specific association of conjunctival and corneal lesions with riboflavin deficiency in man apparently had not been noted prior to the year 1939. It is true that, as noted by Sebrell,¹⁰ early Italian writers on pellagra, notably Soler in 1791 and Rampoldi in 1885, refer to such eye symptoms as inflammation of the cornea and corneal ulcers and opacities. In this country Clark reported pain in the eyes, conjunctivitis, failing vision and iritis in pellagrins, and Whaley mentioned photophobia, mydriasis, and superficial inflammation of the cornea. In the light of present knowledge, these lesions might be interpreted as manifestations of riboflavin deficiency. But the first definite statement relating clinical ocular disease to riboflavin deficiency would appear to be that of Spies, Bean and Ashe in May, 1939. They stated that some patients with riboflavin deficiency complain of a disturbance of vision which disappears in 4 to 6 days following the administration of adequate amounts of riboflavin. This rather indefinite statement is made somewhat more definite in a paper published by Spies, Vilter and Ashe¹² in September, 1939. They called attention to an "undescribed manifestation of a deficiency state," "a lesion of the eyes characterized by bulbar conjunctivitis, lacrimation, burning of the eyes, and failing vision," which yielded to riboflavin therapy. Since that time a number of articles have appeared which describe this syndrome more accurately.

Lesions of the Cornea in Experimental Animals. According to Day, Langston and O'Brien,³ Goldberger and Lillie reported in 1926 that rats on diet deficient in vitamin G developed loss of hair around the eyelids and excess secretion from the conjunctiva; Chick and Roscoe stated in 1927 that young rats showed alopecia around the eyelids followed by conjunctivitis and ophthalmia after several weeks on vitamin G deficient diet; Salman, Hays and Guerrant in 1928 reported lacrimation, ptosis, alopecia of eyelids, conjunctivitis and opaque eyeballs in rats on a similar diet. However, these last authors stated that the cornea was rarely involved and that the opacity observed was usually in the vitreous and sometimes in the lens. Likewise, in 1928, Findlay stated that the corneas remained normal but that alopecia and swelling of the lids and conjunctivitis developed in vitamin G deficient rats. In 1929 Sherman and Sandel¹¹ reported "sore eyes" with alopecia and abnormal secretion from the conjunctiva in their vitamin G deficient rats; and in a later

article in 1931 they included a report by Pappenheimer on the histologic examination of the cornea of one of these rats, "a very slight keratitis with corneal corpuscles, a few neutrophils, and some new-formed blood channels." Also in 1931 Thatcher, Sure and Walker reported that ophthalmia occurred in 15% of rats on a vitamin G deficient diet. Langston, Day and O'Brien reported, also in 1931, on the ocular changes in 37 rats. They found alopecia of the eyelids in 68%, lacrimation in 60%, conjunctivitis in 96%, anterior interstitial keratitis in 100%, and cataract in 94%. During the stage of acute inflammation microscopic examination of the lids showed moderate infiltration of the skin and subcutaneous tissues with lymphocytes and neutrophils and hemorrhagic areas. The corneas appeared clear in some cases, slightly clouded in others, and showed superficial vascularization in most cases. Microscopic examination revealed an inflammatory process in the anterior stroma. The epithelium was normal but small lymphocytic and leukocytic infiltrates accompanied by new vessel formation were found directly under the epithelium. In the later stages the lids were found to be normal except for alopecia, but the corneas showed small areas of scar tissue with new-formed blood-vessels in the anterior stroma visible both on loupe and microscopic examination.

In 1935 Bourne and Pyke² attempted to repeat the observations of Langston, Day and O'Brien on the development of cataract in rats fed a diet deficient in vitamin G. They were able to produce cataracts in only 31% of the animals after a period of 79 days on the diet. They stated that the most consistent ocular symptoms was "superficial keratitis" which occurred within 70 days in 92 to 100% of the rats. In nearly all cases this inflammatory condition cleared up as the experiment progressed, leaving the cornea clear, although vascularization and residual scarring of the cornea were observed in a few cases. In some animals the inflammatory condition recurred.

In 1939 Eckardt and Johnson,⁵ also in the course of a study on nutritional cataract, noted keratitis or vascularization of the cornea in 12 of 23 rats on a riboflavin deficient diet. They were inclined to attribute little importance to these changes since they believed them to be transitory and not characteristic of riboflavin deficiency. However, the specific relationship of these corneal changes to riboflavin deficiency became apparent when, in a second series of animals, it was noted that all rats which survived to the 48th day showed either keratitis or vascularization of the cornea.

A detailed study of the corneal vascularization occurring in rats on diet deficient in riboflavin has been made by Bessey and Wolbach.¹ They state, "Vascularization of the cornea is an early and constant phenomenon in albino rats in riboflavin deficiency. It precedes all other demonstrable lesions of the deficiency." It was found in over 300 rats during a period of more than 2 years. Microscopic examination or India ink injections never failed to show it after the 4th week of riboflavin deficiency. With regard to the progress of the ocular lesions they stated that in 5 to 7 weeks the palpebral fissures become noticeably smaller, the eyeballs appear less prominent and even sunken in the orbits, the

lids become swollen, and a serous, blood-tinged conjunctival discharge develops. The corneas become slightly dull as if finely sanded and by the end of the 10th week the corneas may be turbid or white.

By the end of the 4th week slit-lamp examination shows a marked radial ingrowth of capillaries into the cornea from the vessels of the limbus. By the end of the 10th or 11th week these blood-vessels extend inward more than one-third the diameter of the cornea and some may reach the center. Apparently simultaneous growth takes place from both arterial and venous sources. At first the capillaries lie just beneath the corneal epithelium, but soon others invade the deeper layers of the stroma. Cloudiness of the cornea develops only several days or weeks after vascularization has occurred. Moderate degrees of cloudiness disappear as soon as 12 hours after large doses of riboflavin by mouth. After 2 weeks' treatment with riboflavin blood-vessels can no longer be seen with the slit-lamp but they can still be demonstrated by microscopic examination or India ink injection. They have been observed after 58 days of adequate riboflavin therapy but in diminished numbers, size and length.

The corneal epithelium remains unchanged until late in the deficiency state. It then shows degenerative changes, probably secondary to the lesions in the stroma. Leukocytes, chiefly polymorphonuclears, may be found in small numbers in the corneal stroma within a week or two after the vessels have penetrated the cornea. They gradually increase in numbers and may accumulate beneath the epithelium and later invade the epithelium. Vesicles may form between the superficial and deep layers of the epithelium and necrosis and ulceration of the cornea may be terminal results.

Similar vascularization of the cornea has been observed by Wolbach and Howe in vitamin A deficient rats. However, in these animals the vascularization seemed to occur in association with or following hyperkeratinization of the corneal epithelium and not as a primary growth of vessels as in riboflavin deficiency.

Bessey and Wolbach suggest that the vascularization of the cornea observed in experimental riboflavin deficiency is a response to asphyxiation of the corneal stroma. This view is supported also by Johnson and Eckardt.^{7a,b,c} They state that riboflavin is believed to be an essential constituent of the oxidation system of Warburg's yellow enzyme. Since the cells are incapable of synthesizing riboflavin it must be continually supplied from exogenous sources to replace that lost in the urine and other excretions. It is believed that if hemin substances are not present in a tissue, such as the avascular cornea, oxidation within the cells is accomplished by Warburg's yellow enzyme. Hence, when riboflavin is deficient or absent the oxidation system of the cornea is seriously impaired. Johnson and Eckardt think that proliferation of capillaries from the limbus into the cornea is readily explained as an attempt by the cornea to overcome local asphyxia by bringing available oxygen in the blood into closer proximity with the corneal cells. Regression of the vessels from the cornea when riboflavin is supplied follows the restoration of the Warburg's yellow enzyme system to its normal position in the process of oxidation. Since riboflavin is destroyed when the hydrogen ion concentration of the tissue fluids is on the basic side,

Johnson and Eckardt think that gastric achlorhydria is a factor in clinical riboflavin deficiency. They state also that since riboflavin is inactivated biologically by light, exposure to sunlight hastens vascularization of the cornea.

Keratitis in Clinical Riboflavin Deficiency. In line with the early reports previously mentioned, Sydenstricker, Geeslin, Templeton and Weaver¹³ in November, 1939, in describing their cases of riboflavin deficiency in human subjects, stated that in one of their patients the palpebral and scleral conjunctiva was very red with a small amount of serous exudate from the conjunctival sac and there was extreme photophobia. They did not mention keratitis. About the same time Pock-Steen⁹ reported on the eye symptoms in 109 patients with leiodystonia, sprue, and sprue-like disorders. They all complained of reduced visual acuity during weak light such as twilight and inadequate artificial illumination. This "twilight blindness" differed from nightblindness in that it was not influenced by administration of vitamin A but was greatly improved a few hours after the administration of approximately 1 mg. of riboflavin. Sixty-seven of the patients improved after one injection of riboflavin, 31 improved after a longer period of treatment, and 11 did not improve. Among other symptoms in these patients Pock-Steen mentioned mydriasis, conjunctival irritation, keratitis, and disturbances of accommodation. He attributed the eye symptoms partly to ariboflavinosis and partly to histamine toxicosis.

In January, 1940, Kruse, Sydenstricker, Sebrell and Cleckley¹⁴ reported on the ocular symptoms in 9 patients with clinical ariboflavinosis, in 5 of whom there were evidences of other types of deficiency disease. All 9 patients had cheilosis, 8 a characteristic glossitis, and 3 had seborrheic accumulation at the nasolabial folds. These patients' complaints varied from itching, burning and a sensation of roughness of the eyes with mild to severe photophobia with dimness of vision in poor light and partial blindness. In 8 patients injection of the conjunctiva on the lids and in the fornix was noted. This was accompanied in 5 by congestion of the bulbar conjunctiva with marked circumcorneal injection and gross opacities in the cornea. Slit-lamp studies revealed that the earliest change was a superficial invasion of the cornea by capillaries arising from the anterior ciliary vessels at the nasal and temporal sides of the cornea. Later the capillaries invaded the substantia propria and superficial and interstitial infiltration appeared. These corneal lesions were not benefited by nicotinic acid, thiamin, cevitamic acid, cod-liver oil, or crystalline vitamin A. However, riboflavin caused a regression of the lesions characterized by improvement in subjective symptoms, by diminution in size and occlusion of the capillaries, and by resolution of the superficial and interstitial infiltration. The ocular lesions were noted to recur upon discontinuance of the riboflavin therapy and to regress again upon its resumption. The authors stated also that in 2 patients with syphilis and interstitial keratitis in whom the keratitis was not improving under antisyphilitic treatment, considerable improvement resulted from the administration of riboflavin after antisyphilitic treatment had been discontinued. They thought that the beneficial effect of riboflavin therapy might be

due to the fact that riboflavin deficiency was the real cause of the keratitis and that the syphilis, if it played any part in the etiology, might be only an exciting factor. On the other hand, if syphilis itself were the cause of the keratitis, riboflavin deficiency might militate against the resisting and healing powers of the cornea.

In June, 1940, these same authors reported further observations on 47 patients known to be receiving insufficient riboflavin. The most frequent symptoms were found to be photophobia and diminution of vision not explained by the refractive error or by opacities in the media. The earliest and most common sign of ariboflavinosis was found to be circumcorneal injection due to congestion and proliferation of the limbic plexus. This was found in 45 patients. Actual invasion of the cornea by capillaries arising from the limbic plexus was observed in 37 patients; fine diffuse superficial opacities of the cornea were seen in 18; superficial punctate opacities in 2; interstitial nebulas in 6, and posterior punctate opacities in 2 patients. Vascularization of the cornea was seen to develop first just beneath the epithelium, later at varying depths in the substantia propria, and last just within the endothelium. Increased or abnormal pigmentation of the iris also was noted in 19 cases. This was seen to decrease during treatment. Photophobia, itching of the eyes, and congestion of the limbic plexus disappear usually within 48 hours after the administration of daily doses of 5 to 15 mg. of riboflavin. When extensive vascularization of the cornea had occurred, the time required to empty the vessels varied from 5 to 18 days. The authors believe that this form of dietary keratitis begins always as a superficial or subepithelial vascularization of the cornea, that superficial opacity is apt to follow, and that only later do the invading vessels penetrate the substantia propria. They are not apt to form a posterior plexus unless the deficiency is severe and prolonged. The vascularization of dietary keratitis is predominantly anterior while that of syphilitic keratitis is posterior; but, in the late stages, the two types of keratitis may be strikingly similar in appearance. The authors believe further that "ariboflavinosis is possibly the most prevalent, apparently uncomplicated avitaminosis; it is possible also that it is more easily recognized than others on account of the specific lesions of the eye which occur early in the period of deficiency."

Riboflavin in Rosacea and Other Forms of Keratitis. According to Doggart⁴ in rosacea keratitis the cornea shows grayish-white infiltrates, chiefly involving the superficial layers of the substantia propria, with ill-defined margins and accompanied by large, freely anastomosing vessels continuous with those of the ocular conjunctiva. The epithelium overlying these infiltrates is often eroded so that corneal ulceration begins. Small rounded gray areas of opacity occur frequently in other parts of the cornea remote from the main lesion. Conjunctival vessels may encroach for a varying distance in the cornea all around its circumference. The lesions heal readily but also recur readily and the infiltration goes farther into the cornea with each recurrence. Verhoeff¹⁵ calls attention to the similarity between rosacea keratitis, superficial punctate keratitis, and neuropathic herpetic-like lesions near the periphery of the cornea. It is of interest that according to both these

authors, writing in 1930 and 1915 respectively, improper diet and digestive disturbances are the most common causes of rosacea keratitis. Daggart adds hypochlorhydria and Verhoeff chronic alcoholism to the list of causes.

In May, 1940, Johnson and Eckardt^{7b} called attention to the similarity between rosacea keratitis and the corneal lesions in rats raised on a diet deficient in riboflavin. They treated 36 patients with rosacea keratitis by the addition of riboflavin to the diet. In 32, prompt healing of the corneal lesions took place and no recurrences occurred during the continuance of riboflavin therapy. Four patients responded slowly or not at all and failed to remain free from symptoms. Of the 36 studied, only 2 took adequate amounts of egg, liver and milk in their usual diet. These 2 did not respond to riboflavin therapy and were found to have no free hydrochloric acid in the gastric juice. Johnson and Eckardt had gastric analyses in 11 of their patients with rosacea keratitis. They found 6 of these had normal gastric acids but lived on a diet deficient in foods naturally rich in riboflavin; 2 patients who had adequate amounts of riboflavin in their diet had reduced gastric acids; 3 took a diet deficient in riboflavin and also had achlorhydria. They assumed, therefore, that rosacea keratitis might be a direct result of riboflavin deficiency and that it might develop either from the use of a diet deficient in riboflavin or from the inability to utilize the riboflavin supplied in an adequate diet because of the absence of free hydrochloric acid in the gastric juice or some other factor necessary for absorption.

With respect to the response of the lesions of rosacea keratitis to riboflavin therapy, Johnson and Eckardt state that acute solitary marginal infiltrates with minimal limbal vascularization disappear within 48 hours after intravenous injections of riboflavin or within 72 hours after oral administration has been started. Multiple marginal infiltrates on a site previously involved and more extensive infiltrates in the cornea respond more slowly. In such cases they advise during the first week 9 mg. of riboflavin intravenously daily or every other day. Then Elixir Vitamin B complex is given in amounts so that the daily intake of riboflavin is 3 mg. A diet containing more than the customary amounts of liver and milk is advised.

Johnson and Eckardt also treated a number of patients with active and inactive syphilitic interstitial keratitis for over a year with riboflavin orally, 6 to 9 mg. daily. They did not observe any dramatic disappearance of blood-vessels but thought originally that the response to treatment was satisfactory inasmuch as a far greater number of vessels than usual became empty of blood cells and could be seen only as empty channels with the slit-lamp. Later, however, they were discouraged with regard to the efficacy of this form of treatment when a girl 9 years of age, who had received 6 mg. of riboflavin daily for over 3 months, developed a severe interstitial keratitis in the other eye. They were unsuccessful also in an attempt to produce interstitial keratitis in rabbits infected with syphilis and placed on a diet deficient in riboflavin. These authors were inclined to consider the type of syphilitic keratitis reported by Kruse and his co-workers as responding excellently to riboflavin as a mixed dietary and syphilitic rather than a characteristic syphilitic keratitis.

However, Johnson and Eckardt again call attention to the importance of riboflavin in the metabolism of avascular tissues, like the cornea, in which Warburg's yellow enzyme is effective in transferring hydrogen from the tissue cells to the capillaries at the limbus. To be certain that an insufficiency of oxidative enzymes is not delaying healing they recommend vitamin B complex as supportive treatment in all forms of corneal ulcers. They note also that factors additional to riboflavin are essential to a healthy state of the cornea. They state that György observed that a deficiency of pantothenic acid in the diet of rats caused a high incidence of corneal ulcers which tended to progress to perforation and endophthalmitis. Addition of pantothenic acid to the diet is followed by a definite tendency to healing of these ulcers. Because of the inclusion of pantothenic acid in Elixir Vitamin B complex Johnson and Eckardt recommend this preparation in the treatment of ulcers of the cornea.

Johnson and Eckardt have been able to demonstrate demodectidae (face mites) in the expressed contents of meibomian glands in cases of acute multiple obstruction, the material being placed in a drop of cedar-wood oil or glycerin and viewed immediately under a low-power microscope. György⁶ noted that pediculosis was encountered among experimental rats exclusively in the group fed diets deficient in riboflavin. Administration of riboflavin by mouth was found to cure the pediculosis. The authors suggest, therefore, that riboflavin may be of aid in the treatment of acute meibomitis.

Summary. As a summary, a statement from Sebrell may be quoted: "It therefore appears that at least some of the many cases of keratitis in this country of vague or unexplained etiology even without lip or tongue lesions are due to riboflavin deficiency. This work indicates that unrecognized riboflavin deficiency is perhaps very widespread in this country and is another indication of the probable extent of nutritional disease."

HENRY P. WAGENER, M.D.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF DECEMBER 17, 1940

Some Hitherto Unrecognized Excretion Products of Sulfapyridine and Their Relation to Urolithiasis. JOHN V. SCUDI and HARRY J. ROBINSON (Merck Institute for Therapeutic Research). The mechanism of the urinary elimination of sulfapyridine is more complex than has been postulated heretofore. A mono-hydroxyl derivative of sulfapyridine and its water soluble glucuronide have been isolated from dog urine (Scudi, J. V., *Science*, **91**, 486, 1940). These products are ordinarily measured by diazotization procedures as "free" or unchanged sulfapyridine.

The formation and excretion of these products has been studied in the rat (Scudi, J. V., and Robinson, H. J., *AM. J. MED. SCI.*, in press). Following the administration of the drug there was an increased urinary output of glucuronic acid which indicated that as much as 40% of the "free" sulfapyridine was present as the highly soluble glucuronide. This was confirmed by a study of the ratio of free to acetylsulfapyridine, and a qualitative estimation of the urinary hydroxysulfapyridine.

The excretion of a part of the drug in a soluble form is important in the etiology of acetylsulfapyridine urolithiasis. If the body is deprived of the mechanism whereby this soluble product is formed, the body must detoxicate and eliminate larger amounts of the drug in some other fashion. Following liver damage induced by phosphorus poisoning the glucuronic acid output was no longer augmented by the administration of sulfapyridine. The production of the insoluble acetylsulfapyridine, however, was not depressed. Thus, three injections of phosphorus produced a 60% incidence of uroliths, whereas a control series of rats showed only a 10% incidence of stones at the sulfapyridine dose level studied.

Preliminary studies in man (Scudi, J. V., Ratish, H. D., and Bullowa, J. G. M., *Science*, **89**, 516, 1939), indicate that man and the rat employ the same mechanism for the excretion of sulfapyridine. Thus, liver function should be considered in the etiology of acetylsulfapyridine urolithiasis.

A Self Regulatory Duodenal Mechanism for Gastric Acid Control and an Explanation for the Pathologic Gastric Physiology in Duodenal Ulcer. HARRY SHAY and J. GERSHON-COHEN (Samuel S. Fels Medical Research Laboratory). By a direct approach in the human subject, we have demonstrated the presence in the normal duodenum of a mechanism which is brought into play by a concentration of acid peculiar to the individual. This concentration for any meal is represented by the peak of free acidity reached after the particular meal. When this concentration of acid reaches the duodenum a mechanism is activated that depresses gastric secretion and is responsible for the descending limb of the normal gastric curve.

In the failure of the normal response of such a mechanism, obtunded by the ulceration and inflammation produced by duodenal ulcer, we believe lies the explanation for the high acid extra-gastric curve seen in this disease. That such a failure of response does occur we have demonstrated in duodenal ulcer patients. If we combine our present findings regarding gastric secretion with the influence of the duodenum upon gastric motor function which we have previously described, we have for the first time, in the disturbance of one mechanism an explanation for the characteristic clinical gastric findings in uncomplicated duodenal ulcer—hyperperistalsis, hypertonicity, hypermotility and hypersecretion.

Reactions of Blood-vessels in Moat Chambers in Rabbits' Ears to Renin and Angiotonin. RICHARD G. ABELL and IRVINE H. PAGE (Department of Anatomy, University of Pennsylvania, and Lilly Laboratory for Clinical Research, Indianapolis City Hospital). Renin and angiotonin (Page, I. H., and Helmer, O. H. *J. Exp. Med.*, 71, 29, 1940) were injected intravenously, and the effects upon small blood-vessels in transparent moat chambers in rabbits' ears observed with the microscope.

The injection of 0.2 cc. Ringer's solution was not followed by contraction of any of the vessels. The injection of 0.2 cc. renin was followed by arteriolar contraction. At the time of greatest contraction, 2.8 minutes after the injection, the arteriole photographed constricted to 0.24 its original diameter. The flow of blood through it was not interrupted. The injection of 1 cc. of angiotonin was followed by arteriolar contraction which became greatest 2.5 minutes after the injection. At this time the arteriole had constricted to 0.53 its original diameter. In this case also the flow of blood was not interrupted. No appreciable change in the diameters of the capillaries or venules was produced by either renin or angiotonin. The intravenous injection of 0.05, of 0.037, of 0.025 and of 0.012 mg. epinephrine was followed in each case by arteriolar contraction which stopped the blood flow in the vessels in the chamber.

Further experiments have been made using an angiotonin solution that had been standardized against epinephrine for equivalent blood pressure raising dosage. These indicate that the peripheral constrictor effect of angiotonin is from $\frac{1}{4}$ to $\frac{1}{2}$ as great as that of epinephrine.

Urinary Excretion of Pregnanediol Glucuronidate in the Hypertensive Disorders of Pregnancy. BACHMAN, C., LEEKLEY, D., and HIRSCHMANN, H. (Department of Obstetrics and Gynecology, University of Pennsylvania). The excretion of pregnanediol glucuronidate was investigated in 10 pregnant women who exhibited one or another of the following hypertensive disorders: 1, Pre-eclampsia; 2, mild, uncomplicated chronic hypertensive disease; and 3, severe chronic hypertensive disease complicated during gestation by the development of proteinuria. Output of this compound was abnormally low in the patients belonging

to the first and last of these groups, but was unaffected in those with uncomplicated chronic hypertension. Abnormal depression of excretion was first noted at the time that proteinuria appeared, and was continuously associated with the latter phenomenon during the remainder of gestation.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

MARCH, 1941

ORIGINAL ARTICLES.

OBSERVATIONS ON THE CLINICAL AND FUNCTIONAL COURSE
OF NEPHROTOXIC NEPHRITIS IN DOGS.

By PAUL J. FOUTS, M.D.,

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AND

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NEPHRITIS due to intravenous injection of organ-specific nephrotoxic sera was first described by Lindeman in 1900.¹¹ It has since been reproduced in rats, rabbits and dogs. The observations of Pearce,¹⁴ Masugi,^{12a,b} Arnott, Keller and Matthew² and of Smadel^{17a} have separated true nephrotoxic nephritis from the non-specific renal irritation which may follow the injection of hemolysins. Detailed clinical, functional, immunologic and pathologic observations on the nature and course of nephrotoxic nephritis in rats have been reported by Smadel,^{16a,b} Smadel and Farr,^{17a,b} Farr and Smadel⁷ and Swift and Smadel.¹⁹

The purpose of this communication is to present observations on the course of nephrotoxic nephritis in dogs. Earlier work in this field has been adequately reviewed by the authors cited above, so that no detailed review is presented here.

Methods. 1. *Preparation of Nephrotoxic Serum.* Normal dog kidneys were washed free of visible blood by perfusion under pressure with 0.9% salt solution, chopped and ground in sand. An approximate 20% suspension was made in physiologic salt solution. Rigid aseptic precautions were observed throughout the procedure. Ten cubic centimeters of the suspension were injected into normal hens daily for 3 days of each of 4 weeks. A rest period of 1 week was followed by a repetition of the series of injections. The dog-kidney precipitin titre of the serum was determined at the end of each 4-week period. A high precipitin titre was reached in most instances at the end of 3 or 4 series of injections. The hen's blood was

then withdrawn, the clot separated and the serum passed through a Seitz filter before injection into dogs.

2. *Renal Function.* Renal clearances of phenol red and inulin were determined by the methods described by Corcoran and Page.⁴ Observations of renal blood flow, calculated from the clearances and extraction percentages of phenol red and inulin, were made in which both kidneys had been subcutaneously explanted by the method of Page and Corcoran.¹³ These determinations were made during a control period and at intervals during the progress of the experimental nephritis. The urine volume was measured daily, its protein content found by the method of Shevky and Stafford¹⁵ and the specific gravity determined with a Westphal-Van Slyke balance. Counts of the urinary sediment were made by the method of Addis.¹ Creatinine determinations for the measurement of creatinine clearance were made by an application of the method of Folin and Wu⁸ to the Evelyn photoelectric macro-colorimeter.⁶

3. *Other Determinations.* Red blood counts, determinations of blood hemoglobin and hematocrit index were done in control periods and during the course of the disease. Determinations of blood urea nitrogen (Van Slyke and Kugel²⁰), plasma carbon dioxide and chloride content were made when specially indicated. Arterial pressure was measured by a mercury manometer and femoral arterial puncture, using a No. 20 needle. Electrocardiographic records were obtained during the acute phase of nephritis in 3 instances.

4. *Pathologic Examination.* Tissues secured at autopsy were forwarded for microscopic examination to Dr. Paul N. Harris (Lilly Research Laboratory, Indianapolis, Ind.) and to Dr. Irving Graef (New York University, New York, N. Y.). Some of the observations made by Dr. Graef form the subject of a separate communication.

Results. 1. *CLINICAL.* (a) *Acute Phase.* The first injection of serum caused no immediate symptoms, although subsequent injections were usually followed by anaphylactic reactions of varying intensity. In one instance (Dog 4) two injections of normal serum were given, the second of which provoked symptoms of anaphylaxis. Neither injection of normal serum had any other effect.

The onset of nephritis occurred from 6 to 10 days after the first injection of potent serum and was ushered in by loss of appetite, lethargy, proteinuria and hematuria. Hematuria was grossly visible in 4 of the 6 subjects, while in the other 2 (Dogs 1 and 6) its presence was only determined by counts of the urinary sediment. Peripheral edema occurred at the onset of the disease in the 2 dogs which later died of nephritis. The explanted kidneys were seen to be greatly swollen during the acute stage of nephritis in these 2 cases. Mild polyuria with a decrease of urinary specific gravity occurred in every instance. Marked loss of weight developed in all but the subject in which nephritis was mildest (Dog 1). The lost weight was regained in those cases in which recovery occurred. Arterial pressure was not increased in any animal, either during the acute or chronic phases of the disease. The ocular fundi were unchanged.

(b) *Subsequent Course.* Complete recovery was observed twice (Dogs 1 and 3). Subsequent injections of potent serum in these

cases failed to reproduce the acute disease. Partial recovery occurred in 3 instances. One of these died of anaphylactic shock during the fourth injection of serum (Dog 2), so that recovery might have occurred in this case also. Dog 4 recovered appetite and apparent well-being, but continued to excrete large amounts of urinary protein. This chronic phase followed repeated injections of large doses of active serum. Dog 5, which received only one injection of nephrotoxic serum, showed partial recovery of weight and appetite and, although hematuria disappeared, proteinuria continued. Edema was present in this case for about 2 months after the first injection. Following the second injection of serum, edema returned, proteinuria increased and appetite and weight were lost. Nephritis was most severe in Dog 6. Appetite did not return with recession of acute nephritis in this case and, although edema persisted, weight showed a progressive decrease. Hematuria and proteinuria never completely subsided in this dog.

(c) *Renal Failure.* Failure of excretory function was evidenced by increases of blood urea nitrogen. This occurred during acute nephritis in every instance. However, renal failure during acute nephritis was not associated with severe prostration nor with symptoms of the uremic state. The serum carbon dioxide content during acute nephritis in Dog 6 was 15.03 and 16.4 mM. per liter on occasions when blood urea nitrogen was 186 and 206 mg. per 100 cc., respectively. The serum chloride was equivalent to 599 and 620 mg. of NaCl per 100 cc.

Renal failure with nitrogen retention, acidosis and symptoms of uremia occurred terminally in Dogs 5 and 6. The course of Dog 6 in some respects resembled that of terminal glomerulonephritis in man. The blood urea nitrogen had remained elevated since the phase of acute nephritis. About 3 weeks before death the edema increased and blood urea rose. There was almost complete loss of appetite and occasional vomiting. Ten days before death the blood urea nitrogen was 180 mg. per 100 cc., and serum carbon dioxide content was 10.6 mM. per liter. Hiccough and repeated mild convulsions preceded coma which developed on the day before death. The blood urea nitrogen at this time was 301 mg. per 100 cc. and the serum carbon dioxide content was 5.54 mM. per liter. The coma, convulsions, odor of the breath, hiccoughs and character of respiration resembled terminal uremia in man.

The final course was much more rapid in Dog 5, which died 35 days after a second injection of serum. Renal function rapidly decreased during the week before death and, as the blood urea rose, the animal rapidly lost weight and became prostrated. The dog was very weak and intensely dyspneic on the day of death and vomited large amounts of bloody fluid. There was oxygen unsaturation of the arterial blood, severe failure of peripheral circulation, intense hemoconcentration and marked arterial hypotension. Blood

urea nitrogen was 216 mg. per 100 cc., serum carbon dioxide content was 12 mM. per liter and serum total protein content 9.42 gm. per 100 cc.

2. ANEMIA. The first injections of nephrotoxic serum caused immediate falls in red cell count, hemoglobin and hematocrit index and a definite increase of plasma bilirubin. Leukocytosis up to 38,000 occurred as anemia developed. These observations suggest that hemolysins were present in the nephrotoxic sera in spite of the precautions used in the preparation. Titration of the most hemolytic serum against the red blood cells of 2 normal dogs showed that hemolysis occurred in dilutions up to 1/64 and 1/120, and that there was slight clumping of the red cells in dilutions up to 1/512 and 1/1024. This serum contained precipitins against the filtrate of dog kidney in dilutions up to 1/100,000.

The numbers of reticulocytes increased moderately after anemia appeared. The degree of reticulocytosis was less than would have been expected from the severity of the anemia. The blood count remained low during the acute phase of nephritis, but returned towards normal parallel to the improvement of renal function in 4 out of the 6 cases. Recovery of this type did not occur in Dog 2. Both red blood count and renal function remained low in Dog 6, in which the anemia became more severe as uremia developed.

Injection of nephrotoxic sera after recovery from acute nephritis caused no recurrence of anemia.

3. Sedimentation rate was slightly increased during the acute phase but returned towards normal with the recovery of renal function.

4. The plasma protein content was not decreased in any case.

5. Electrocardiographic records obtained during the height of acute nephritis showed no abnormalities.

6. RENAL FUNCTION. The onset of nephritis was associated with development of marked disparity in the renal clearances of phenol red and inulin. One or 2 days before proteinuria reached its peak during the acute phase, phenol red clearance was at or above control levels. The simultaneous clearance of inulin was absolutely or relatively depressed, so that the phenol red/inulin clearance ratio was increased. Inulin clearance continued to fall during the next 6 to 12 days, and phenol red clearance fell in all but the mildest case (Dog 1). The rate of fall of phenol red clearance was less rapid than the decline of inulin clearance in all cases but Dog 6, in which nephritis was most severe. The phenol red/inulin clearance ratio was high during the progress of acute nephritis in all but the severest case.

Some recovery of renal function occurred within 14 to 28 days of the first injection of serum in every case. The recovery of inulin clearance usually preceded the rise of phenol red clearance by 1 to 3 days. The absolute and relative values of renal clearances of phenol

red and inulin returned to normal in those cases in which recovery became complete (Dogs 1 and 3). Proteinuria disappeared in the recovered subjects.

The clearances had fallen to such a low level in Dog 6 that, although some temporary recovery occurred, life was maintained for only $2\frac{1}{2}$ months when uremia developed. Clearances of phenol red and inulin returned to and above control levels in Dog 4. The ratio of phenol red/inulin clearance remained high in this case and proteinuria persisted for more than 1 year. During the last 3 months of this period the phenol red clearance has fallen, so that the clearance ratio is low. Partial recovery with continued proteinuria and high phenol red/inulin clearance ratios was also observed in Dog 2, which died of anaphylactic shock during the fourth injection of nephrotoxic serum.

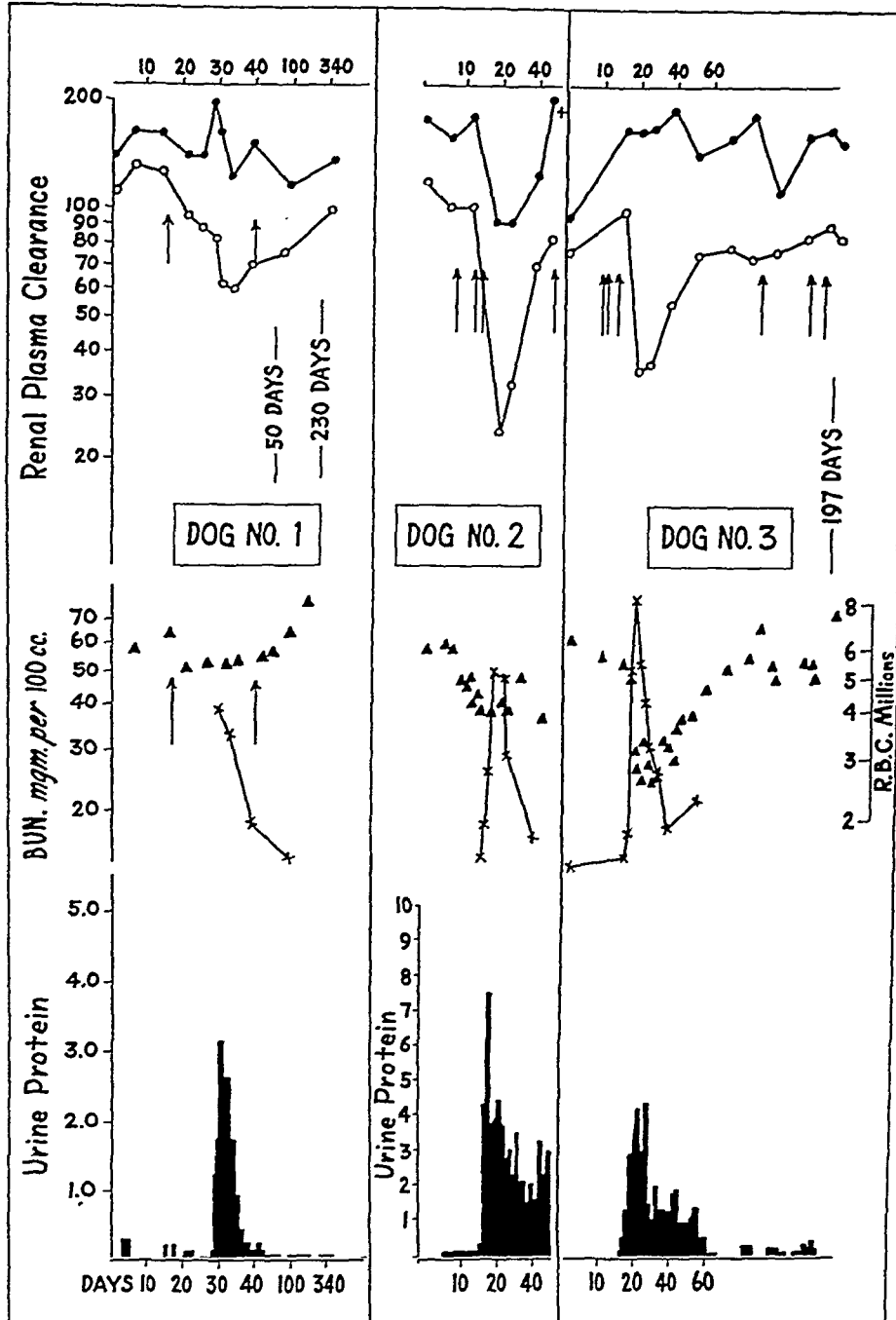
Partial recovery with continued proteinuria and high clearance ratios was observed over a longer time in another case (Dog 5), in which clearances were unaltered 10 days after the second injection of serum, though proteinuria had increased. Both phenol red and inulin clearances were greatly depressed at the next observation, 30 days after injection, and a further precipitous fall of renal function occurred during the next 3 days, resulting in death in uremia.

The observations on the 2 subjects with subcutaneously explanted kidneys (Dogs 5 and 6) are of particular interest since they include measurements of renal extraction percentages (renal arteriovenous phenol red and inulin differences) and renal blood flow. Renal blood flow increased in both cases at the onset of nephritis. The fall of phenol red clearance which occurred later in the acute phase paralleled a decrease in renal blood flow. Both phenol red clearance and renal blood flow later partially returned towards normal in the subject in which mild chronic nephritis had been produced (Dog 5). The renal blood flow remained at a low level in the other subject (Dog 6). The decrease in renal blood flow in both cases was not as great as the decrease of clearance. Renal extraction percentages in general varied in the same direction as their respective clearances.

Blood urea nitrogen increased during the acute phase of nephritis and either returned or tended towards normal as clearances increased.

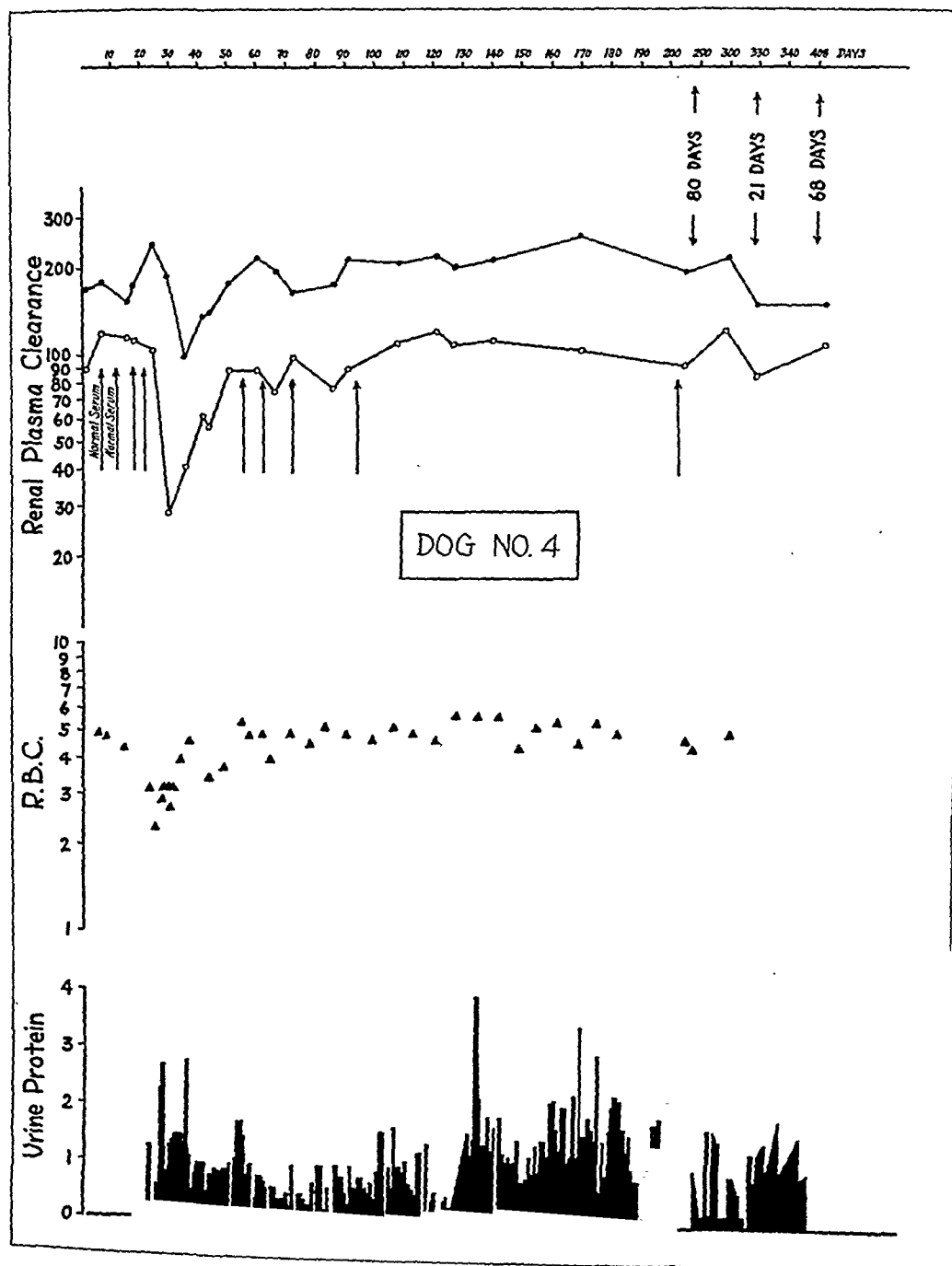
The average of 6 determinations of the proportion of urea reabsorbed from glomerular filtrate ($1 - \frac{\text{urea clearance}}{\text{inulin clearance}}$) 100 during acute nephritis was 52%. Normal reabsorption of urea from glomerular filtrate in the dog is about 43% (Van Slyke, Hiller and Miller²¹).

Since creatinine diffuses more rapidly than inulin (Bunim, Smith and Smith³), loss of the normal barrier to reabsorption of creatinine should result in depression of creatinine clearance relative to the simultaneous clearance of inulin. Creatinine and inulin clearances

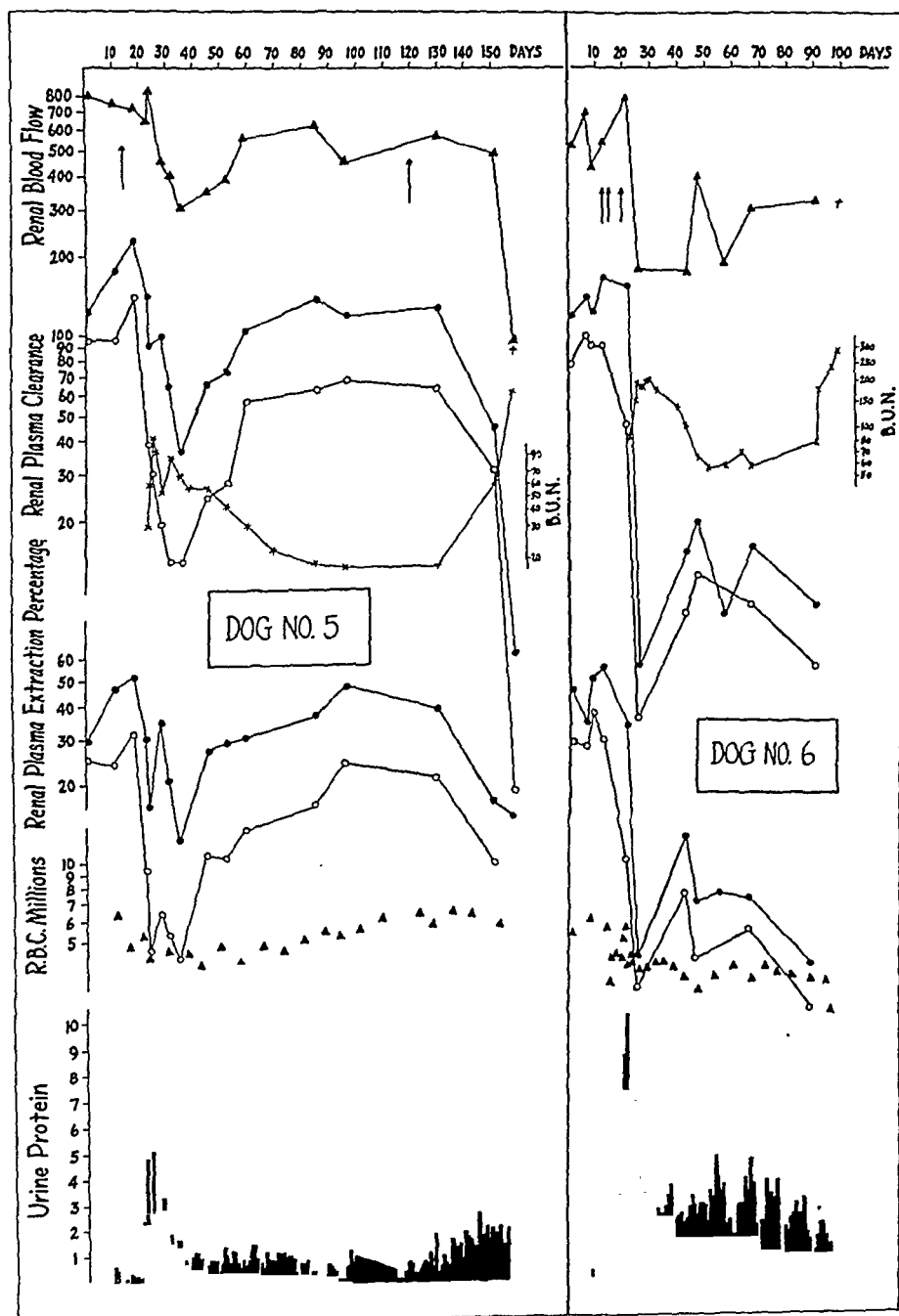


●—● Plasma phenol red clearances or extraction percentages; ○—○ Plasma inulin clearance or extraction percentage; ▲—▲ Renal blood flows averaged from renal blood flows separately calculated from hematocrit, plasma phenol red and inulin clearances and plasma extraction percentages. Renal blood flows and plasma clearances and extraction percentages are expressed as cubic centimeters per square meter of body surface per minute; ×—× Blood urea nitrogen (B.U.N.) in milligrams per 100 cc; ▲ Red blood cells (R.B.C.) in millions per c.mm. Renal blood flows, plasma clearances and extraction percentages, blood urea nitrogen and red blood cell counts are plotted semilogarithmically against the days of observation. Urine protein is shown by the blocked area in grams per 24 hours and charted arithmetically against the days of observation. Injections of serum are indicated by vertical arrows. The sign † indicates day of death.

were simultaneously determined on 2 occasions in Dog 4 during acute nephritis. The values of the creatinine/inulin clearance ratios were respectively 1.02 and 0.985. These values are identical with those observed in normal dogs (Smith¹⁸).



7. PATHOLOGIC EXAMINATION. Autopsies were done in 3 cases (Dogs 2, 5 and 6). A renal biopsy was done in Dog 5 during the height of acute nephritis. The findings in the pathologic examination of these tissues form the subject of a separate report. It is sufficient for the purpose of this communication to note that the



findings in Dog 2 and the biopsy of Dog 5 are those of acute intercapillary glomerulonephritis. Swelling of the glomerular basement membrane also was present in Dogs 5 and 6. In these, however, scarring and hyalinization of the glomeruli and extensive degeneration and calcification of tubular areas had occurred.

Discussion. 1. *Mechanism of Nephritis.* Smadel^{16a} from studies of nephrotoxic nephritis in rats, states that the organ-specific antibodies which cause swelling of the intercapillary substances of the glomerular tuft and tubular degeneration without hematuria differ from the substances which excite anaphylactoid reactions, transient proteinuria, hematuria and deposition of fibrin thrombi in the glomerular capillaries. This distinction of nephrotoxic nephritis from the specious nephritis due to injection of serum containing antibodies other than nephrotoxin was first suggested by Pearce.¹⁴ Neither Smadel^{16a} nor Pearce¹⁴ observed hematuria in true nephrotoxic nephritis unless massive doses of nephrotoxin were given. The urinary and clinical findings of the transient "false" nephritis appear immediately after injection and are usually accompanied by anaphylactoid reactions.

The first injections of nephrotoxic sera in dogs caused immediate intravascular hemolysis in each of our cases. The onset of nephritis, with renal hyperemia (increased renal blood flow) hematuria and proteinuria occurred 6 to 10 days later. It is therefore probable that the hematuria and other renal changes which we observed are not due to factors associated with the hemolytic reaction.

Anaphylactic reactions occurred only with injections subsequent to the first and, unless the injection was given within a week of the first administration of serum, were not associated with recurrence of intravascular hemolysis. Severe anaphylactoid reactions occurred in Dogs 1, 3 and 4 on injection of potent serum after recovery from acute nephritis. These reactions did not provoke exacerbations of nephritis. It may be noted that the second injection of normal non-nephrotoxic hen serum in Dog 4 likewise caused an anaphylactoid reaction, but without evidence of renal irritation. In another instance, serum given as an initial injection to Dog 5 caused chronic nephritis without any anaphylactoid reaction, while serum from the same donor given Dog 4 as the fourth and fifth injections resulted in severe anaphylaxis. The same serum when given as the seventh injection (Dog 4) caused no reaction.

The anaphylactic reaction in the dog is therefore distinct from the hemolytic reactions to first injections.

Neither the hemolytic nor the anaphylactoid reactions appear to be concerned with the development of the nephrotoxic nephritis which we have observed in dogs. It is therefore probable that the phenomena observed in the course of nephrotoxic nephritis in dogs, including hematuria, are phases in the reaction to organ-specific nephrotoxins.

It is of interest to note that the onset of nephrotoxic nephritis in the rabbit (Kay and Longcope¹⁰) may be prevented by Roentgen irradiation of the animal after injection of serum. It is suggested that the nephrotoxic reaction is secondary to the formation of nephrotoxin-kidney combinations. The immune response to the donor's serum injures the kidney which was immunologically altered but had remained structurally intact. Roentgen irradiation is believed to inhibit the formation of antibodies and thus prevent the onset of nephritis.

2. *Effects of Repeated Injections.* Two or more injections of serum were given in most instances before the appearance of nephritis. However, the experience in Dogs 1 and 5 establishes that one injection is adequate for the production of nephrotoxic nephritis, either mild or severe. Repeated injections after subsidence of nephritis in Dogs 1 and 3 were apparently ineffective. The injections given Dog 4 may possibly have contributed to the chronicity of nephritis in this case, although a single injection resulted in chronic nephritis in Dog 5.

These observations on the effect of repeated injections contrast with the single experience in Dog 5 in which the second injection of serum caused an anaphylactoid reaction, increased proteinuria and a return of edema, although there was no evidence of hemolysis. Renal function, which in this case was unaltered 10 days after the injection, had fallen markedly at the end of 31 days and continued to fall until the dog's death in uremia 35 days after the second injection. At autopsy there were numerous fibrin thrombi in the glomerular capillaries. The long delay in the appearance of renal failure makes it difficult to attribute this course to the anaphylactic reaction. We are therefore tempted to attribute it to the effect of nephrotoxic serum.

3. *Changes of Renal Function.* Increased renal blood flow was observed at the outset of acute nephritis in the 2 cases in which this function was measured. Renal blood flow was probably increased in at least 2 other subjects in which phenol red clearance increased above control levels at this time. Acute nephrotoxic nephritis, like most inflammatory reactions, at its outset is associated with hyperemia.

Both in the acute and chronic phases of nephritis inulin clearance was abnormally depressed in relation to the clearance of phenol red. This depression of inulin clearance might conceivably be due to tubular reabsorption of inulin by diffusion through damaged and incompetent tubular cells. Reabsorption of inulin apparently does not occur in normal dogs (Smith¹⁸). That reabsorption of inulin did not occur in dogs suffering from nephrotoxic nephritis is suggested by the observations that urea reabsorption is only slightly increased and that creatinine is apparently not reabsorbed at all. The depression of inulin clearance therefore reflects a decrease in

the proportion of water filtered from plasma as it passes through the kidneys.

This depression of glomerular filtration must be due either to decreased intraglomerular pressure or to decreased efficiency of filtration. The presence of proteinuria and, more directly, the swollen intercapillary substance found in glomerular capillaries at the height of acute nephritis and in chronic phases suggest that the decrease in filtration resulted from the thickening of the filtering surface and not from altered renal hemodynamics. One may conceive of a state in which glomerular capillaries are so altered by inflammatory change that they permit the passage of protein as it were through abnormal pores, but retain water and the solutes of plasma because swelling has reduced their effectiveness as filters.

Many glomeruli which at the outset of nephritis were patent, although filtering inefficiently, became occluded as inflammation continued. Renal blood flow and phenol red clearance fell at this time. The fall of inulin clearance was more rapid, possibly because swelling interferes with filtration before it occludes the glomerular capillaries. The renal tubules were ischemic at this time. It should be noted, however, that renal blood flow did not decrease as rapidly as clearance; that is, that the proportion of blood perfusing non-excretory tissues is increased. This observation suggests that shunts were opened around some of the occluded glomeruli.

As inflammation receded, the process was reversed so that blood flow increases and filtration becomes more efficient. Some or many glomeruli remain closed by scarring (Dogs 5 and 6) so that their tubules atrophy completely. The inflammatory process did not always entirely subside, but continued in some cases (Dogs 4, 5 and 6).

The fact that the capacity of the tubular cells to secrete phenol red was apparently unimpaired in the initial acute phase at a time when glomerular function was decreased suggests that the renal lesion of nephrotoxic nephritis is primarily glomerular and raises the possibility that the tubular lesions which subsequently appear occur as the result of ischemia due to glomerular occlusion. Observations by Ehrich, Wolf and Bartol⁵ of the excretion rates of cyanol and azofuchsin in rabbits during the acute phase of nephrotoxic nephritis have also demonstrated the preponderance of glomerular as opposed to tubular injury. Their morphologic observations indicate that renal hyperemia occurred during the acute phase of nephrotoxic nephritis in rabbits.

4. *Anemia.* The anemia which occurred abruptly after injection of nephrotoxic serum was at its onset due to hemolysins. The reticulocytosis which followed was less than would have been expected from the degree of anemia. The red blood count remained at a low level during acute nephritis and only tended towards normal as renal function improved. Anemia continued in the one case in which

renal function remained severely impaired (Dog 6). The development of uremia in this case was accompanied by a further decrease in red cell count. Complete cure of the anemia occurred in those cases in which full recovery occurred. These observations strongly suggest that the activity of the bone marrow was depressed during the period of severe renal disease.

5. *Comparison With Nephrotoxic Nephritis in Rats and Rabbits.* The clinical and functional course of nephrotoxic nephritis in rats has been reported by Farr and Smadel.⁷ The onset of nephritis in rats follows the injection of nephrotoxic serum sooner than it does in the dog. Hematuria does not occur unless massive doses of nephrotoxin are given and in the acute reactions to anaphylactoid and hemolytic factors. Cylindruria is very intense. Urea clearance is decreased in acute nephritis and in those cases in which chronic disease is established. Hypertension and cardiac hypertrophy occur in some cases. Edema was noted during acute nephritis. Hypoproteinemia was found in some cases during the acute phase and in those progressive cases which went on to uremia.

In the rabbit (Ehrich, Wolf and Bartol⁸) the onset of nephrotoxic nephritis occurred 1 week after injection of serum and was characterized by oliguria, proteinuria, hematuria, cylindruria, edema and increase in urea nitrogen.

Nephrotoxic nephritis as it was observed in the dog differs from that which occurs in the rat in many respects but resembles the course observed in rabbits. Hematuria was the rule in every case of acute nephritis in the dog. Hypertension did not develop in any case. Although edema was present in 2 cases and persisted and recurred in the chronic nephritis of Dog 6, there was no decrease in plasma protein at any time. The course of nephritis in the dog seemed to tend towards the extremes of rapid recovery or of chronic nephritis with reduction of renal function.

The variations of nephrotoxic nephritis in different species may be due to inherent differences in their reactions to nephrotoxin, or to alterations in the potencies and methods of administration of the sera.

6. *Comparison With Nephritis in Man.* The onset of nephrotoxic nephritis in dogs greatly resembles that of acute hemorrhagic Bright's disease in man. The course of the anemia in the dog was not dissimilar from that observed in nephritis in man. However, neither hypoproteinemia nor hypertension developed during the course of nephrotoxic nephritis in the dog.

Observations in cases of Bright's disease in human beings suggest that renal blood flow is increased and filtration depressed in the acute phase (Goldring and Smith⁹). Reduction of renal blood flow with abnormal depression of filtration may occur as the disease progresses. Increase of renal blood flow with restoration of normal filtration has been observed during recovery in Bright's disease in human beings. These observations are exactly paralleled in our results.

It may be concluded that the clinical and functional alterations of nephrotoxic nephritis in dogs, rats and rabbits, although varying somewhat in these species, together closely simulate many aspects of Bright's disease in human beings.

Summary. Anti-dog kidney nephrotoxic serum was prepared by repeatedly injecting hens with sterile emulsions of dog kidneys. Injection of these sera in dogs, after a quiescent period of 6 to 10 days, resulted in the onset of hematuria, proteinuria and loss of appetite. Renal blood flow was increased at this time and the efficiency of glomerular filtration was reduced, although the integrity of the tubules was apparently maintained. It is suggested that the increase of renal blood flow is due to inflammatory hyperemia, while the decrease in filtration is due to thickening of the glomerular basement membrane. As the glomerular swelling increases, the capillaries are occluded so that renal blood flow decreases. The decrease in renal blood flow is less rapid and severe than the decrease in clearance, so that it is suggested that shunts may have opened around some of the occluded glomeruli.

Subsidence of the inflammatory reaction is associated with reversal of this process, although scarring may result in permanent occlusion of some glomeruli and complete atrophy of their tubules. Chronic nephritis is established in some cases.

Repetitions of the injections of nephrotoxic sera do not usually result in exacerbation of nephritis.

Hemolytic anemia, apparently due to hemolysins not eliminated from the sera by the precautions used in their preparation, occurred immediately after the first injections of serum. The delay in appearance of nephritis after the hemolytic reaction and the course of the renal lesion indicate that it was not due to the hemolytic reaction.

The reticulocytosis which followed the development of anemia was less than would have been expected from the degree of anemia. The course of the anemia subsequent to the development of nephritis varied in the same direction as the changes of renal function. These observations indicate that the activity of the bone marrow was depressed during the existence of severe renal damage.

Although the courses of nephrotoxic nephritis in dogs, rats and rabbits show some differences between these species, the clinical and functional alterations which occur in these species together mimic many phases of Bright's disease in human beings.

Conclusions. 1. Nephrotoxic nephritis due to injection of relative organ-specific nephrotoxic sera in dogs is at its onset associated with increased renal blood flow and decreased efficiency of glomerular filtration.

2. The decrease of glomerular efficiency is apparently due to thickening of the glomerular basement membrane. This functional alteration persists during the course of active nephrotoxic nephritis. Its presence is indicated by an increase in the ratio of phenol red to inulin clearance.

3. The hematuria which is observed at the onset of nephrotoxic nephritis in the dog and during the persistence of severe chronic nephritis is apparently not related to hemolytic or anaphylactic reactions which may follow the injection of sera.

4. Although the acute anemia which followed injection of nephrotoxic sera in dogs is due to hemolytic factors present in the sera, the course of the anemia subsequent to the development of nephritis suggests that depression of bone marrow activity is present during the persistence of severe renal disease.

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THE INFLUENCE OF LIVER DAMAGE ON THE PLASMA PROTHROMBIN CONCENTRATION AND THE RESPONSE TO VITAMIN K.*

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MANY reports have appeared regarding the efficacy of vitamin K to elevate the lowered plasma prothrombin concentration observed in various disease conditions, particularly obstructive jaundice. Nevertheless, there have been encountered some patients suffering from obstructive jaundice who have failed to respond to the administration of vitamin K. Since many patients afflicted with chronic diseases of the liver have likewise been noted to have hypoprothrom-

* Aided by a grant given in memory of Laurence A. Myers, Jr., and Thomas J. Maxwell, and by a grant from the Christine Breon Fund.

We wish to acknowledge the assistance of Lucile Hook Hamlin, of the Department of Hygiene, University of California, Berkeley, in the preparation of the statistical analysis.

binemia refractory to vitamin K therapy, there has been a tendency to ascribe all therapeutic failures to liver damage.

Certain experimental observations suggest that the liver is concerned in the production of prothrombin. It has been observed that the plasma prothrombin concentration may be diminished and does not respond to the administration of vitamin K in acute liver necrosis induced by chloroform, phosphorus and carbon tetrachloride poisoning in dogs^{16c,21,29} partial hepatectomy in rats,^{28a} total hepatectomy in dogs,^{3,30} trauma to the liver in dogs¹¹ and subhepatic abscess in rats.⁸

Inquiries have been made in regard to a possible correlation between the prothrombin concentration and the results of various liver function tests. There has been general agreement that no significant relationship exists between the prothrombin concentration and the plasma fibrinogen content, the bilirubin level, the results of the bromsulfalein dye clearance or oral galactose tolerance tests. Some data have been presented to indicate a parallelism between the results of the hippuric acid test and the prothrombin concentration. Quick observed 1 patient with obstruction of the common bile duct due to adhesions, who had hypoprothrombinemia and an hippuric acid test 51% of normal, and who was refractive to vitamin K therapy. After the jaundice had disappeared, and the prothrombin concentration had returned to 100%, the hippuric acid test was 77% of normal.^{16c} In 36 tests on normal subjects and patients known to have liver disease, exclusive of biliary obstruction or fistulae, Wilson³¹ noted a high correlation between the hippuric acid excretion and the plasma prothrombin concentration. In the cases presented by Stewart and Rourke,^{26a} the hippuric acid excretion varied from 0.6 to 6.7 gm. (average 3.3 gm.) in 15 patients with obstructive jaundice due to stone in the common bile duct and from 0.2 to 5.8 gm. (average 3.1 gm.) in 9 patients with obstructive jaundice due to carcinoma. They also stated that "There is, on the whole, agreement between clinical appraisalment of the patient's condition, the results of liver function tests and the extent of prothrombin deficiency. Further study may indicate that the prothrombin depression is a better index of liver damage than other standard liver function tests."

Pohle and Stewart¹⁵ stated that their group of 18 patients who failed to respond to vitamin K was composed of ". . . patients in whom liver function tests or histopathological studies, or both, revealed extensive damage to the liver parenchyma. Similar studies showed no indication that hepatic damage of this degree was present in the group of 28 patients who responded satisfactorily."

Smith and co-workers²² stated that, "When the liver is partially excised or is injured by poisons, infection or tumor growth, the level of plasma prothrombin falls. In these cases there is no vitamin deficiency, and feeding vitamin K does not cure the condition."

Butt and co-workers⁶ likewise observed patients with severe liver damage who failed to respond to vitamin K. They stated that, "We have observed that patients who have an elevated prothrombin clotting time but who do not respond to the administration of these antihemorrhagic substances, are patients in whom the liver is very badly damaged. In fact, the failure to respond to such substances is, in itself, indicative of hepatic deficiency." On the other hand, they^{5b} observed that, "Actually, even a badly damaged liver is capable of synthesizing prothrombin; we have records of patients who presented every known clinical evidence of hepatic insufficiency and who have exhibited maximal degrees of physiologic disturbance (as determined by studies of hepatic function) who have been able to absorb and utilize vitamin K and maintain normal values for the concentration of prothrombin in the blood."

A review of published reports^{1b,2,4,5b,c,6,9,11,13,15-19,21-30} reveals that some patients afflicted with diseases of the liver do not have hypoprothrombinemia, some have a low prothrombin concentration which is elevated following the administration of vitamin K and some are completely refractive to vitamin K therapy.

It is evident that there is some confusion in the clinical evaluation of the influence of liver damage on the prothrombin concentration. The present investigation was conducted in order to study the relationship between the prothrombin concentration and liver function as determined by various liver function tests. Emphasis has been placed on the hippuric acid test^{16a} since it is simple, inexpensive, and can, with few exceptions, be performed on all patients. The excretion of 4.5 gm. of hippuric acid in 4 hours following the ingestion of 6 gm. of sodium benzoate is considered normal. Plasma prothrombin concentration was measured by the method of Quick.^{16c} The prothrombin times for full strength and half strength test plasmas were converted to prothrombin concentrations by comparison with the dilution curve of normal plasma. When the prothrombin time of a blood specimen was equal to or shorter than the normal control, the prothrombin concentration was taken as twice the value obtained for the half strength plasma. In all other instances the values expressed are the averages obtained for the prothrombin concentration of full strength plasma and twice the value obtained for the prothrombin concentration of half strength plasma. Duplicate tests were done on all specimens, and readings were recorded to the nearest 5%. In addition, the bleeding time,¹⁰ the coagulation time¹⁴ and the clot retraction index^{1a,12} were done in all cases. All tests were performed by the authors.

Three synthetic vitamin K compounds were employed. Phthicol* (2-methyl-3-hydroxy-1,4-naphthoquinone) was administered intravenously in doses of 50 to 300 mg. of 0.5% solution. Vitamin K₅† (4-amino-2-methyl-naphthol hydrochloride) was administered intra-

* Made available through the courtesy of the Galen Company, Berkeley, Calif.

venously in doses of 5 to 30 mg. of 0.1% solution. Gelatin capsules containing 0.6 mg. vitamin K₃* (2-methyl-1,4-naphthoquinone) dissolved in corn oil were administered orally in daily doses of 3.6 to 5.4 mg. The total daily oral dose was divided into three equal parts and given after meals. Deoxycholic acid (100 mg.) was given with each dose of vitamin K₃. In order to attain the maximum prothrombin concentration as rapidly as possible, larger than minimal effective doses of these compounds were used. Adequate thera-

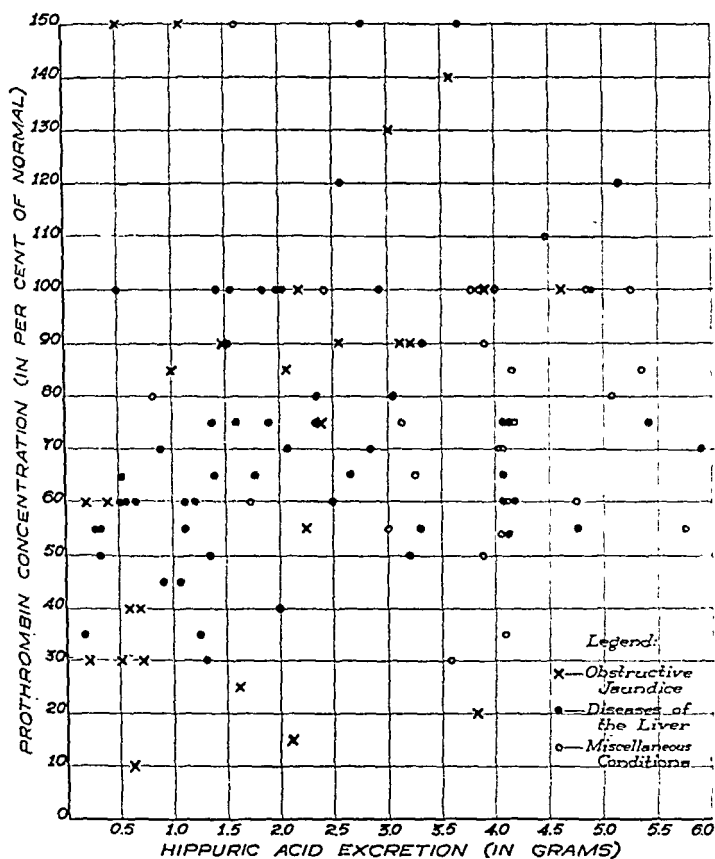


Fig. 1.—Relation between the oral hippuric acid and the plasma prothrombin concentration tests in 92 patients not treated with vitamin K.

peutic results have been obtained in some cases with phthiocol in dosage of 25 mg.,^{5b} with vitamin K₅ in dosage of 2 mg.²⁰ and with vitamin K₃ in dosage of 1 mg. daily.¹⁸

Graphs showing the results of our study are given in Figures 1 and 2. With the exception of 2 cases in which the elevation of the prothrombin concentration was delayed, all observations on the same patient were carried out within a period of 4 days.

* Made available through the courtesy of Parke, Davis and Company, Detroit, Mich. Numerical designations given by the manufacturer.

In Figure 1 is given the values for the prothrombin concentration and hippuric acid tests in all patients, none of whom had received vitamin K. One hundred and eight tests were done on 92 patients, 23 of whom had obstructive jaundice, 43 diseases of the liver and 26 miscellaneous non-renal diseases. In Figure 2 is given the values for the prothrombin concentration and hippuric acid tests on selected patients after treatment with vitamin K. Twenty-seven tests were done on 25 patients, 11 of whom had obstructive jaundice, 12 diseases of the liver and 2 miscellaneous non-renal diseases.

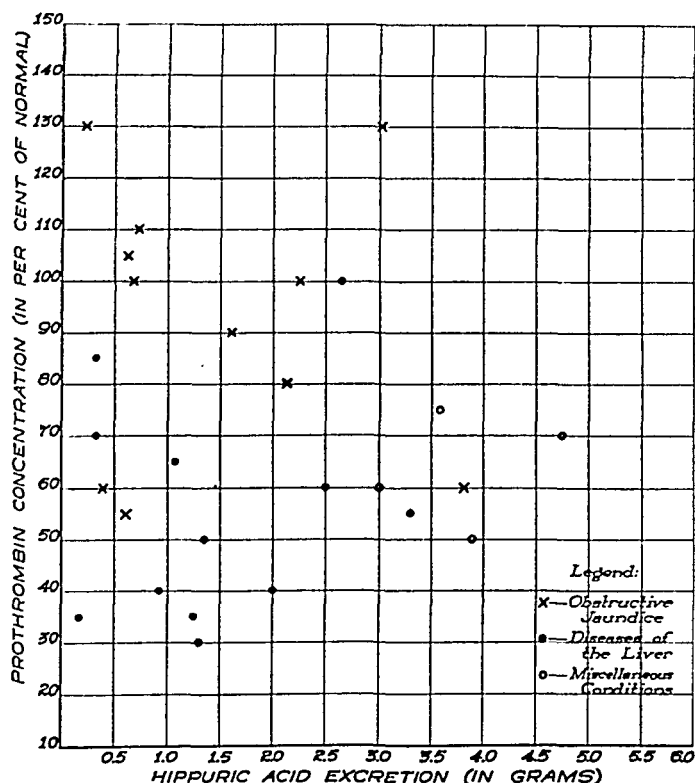


FIG. 2.—Relation between the oral hippuric acid and the plasma prothrombin concentration tests in 25 selected patients after treatment with vitamin K.

In Table 1 is recorded the statistical analysis of the results of the hippuric acid test and the prothrombin concentration. In every sample there was no significant correlation between hippuric acid excretion and prothrombin concentration. From these analyses it may be assumed that the factor which produces alterations in the excretion of hippuric acid does not operate to affect the prothrombin concentration. In addition to the hippuric acid test, the excretory function of the liver was measured by the rose bengal test⁷ in 41 patients without jaundice. In normal individuals not more than 60% of the dye is retained in the blood stream in 8 minutes and not

more than 40% in 16 minutes. This test is of minimal value when jaundice is present, and for this reason it was not done in patients with biliary obstruction or acute diseases of the liver. A summary of the comparative results of the tests is given in Table 2. Insofar as the average values of the hippuric acid tests are concerned, there appears to be good agreement with those of the rose bengal test, however, in individual instances there was sometimes wide variation between the results of the two tests.

TABLE 1.—CORRELATION COEFFICIENTS BETWEEN THE HIPPURIC ACID TEST AND THE PLASMA PROTHROMBIN CONCENTRATION IN 92 PATIENTS.

Sample.	Description of sample.	No. of tests.	Correlation coefficient.
A	Total sample	108	+0.2040
B	Sample A reduced by excluding all tests on patients with obstructive jaundice (26) or sprue (1)	81	+0.2270
C	Sample B reduced to 15 patients who were to receive vitamin K	15	+0.4868
D	Same as sample C after the administration of vitamin K	15	+0.1942
E	Sample A reduced to tests on patients with obstructive jaundice (26) or sprue (1)	27	+0.2695
F	Sample E reduced to 12 instances in which vitamin K was to be given	12	+0.2246
G	Same as sample F after the administration of vitamin K	12	-0.1130
H	Combined samples C and F	27	+0.2783
I	Combined samples D and G	27	-0.0414

TABLE 2.—COMPARATIVE RESULTS OF THE ROSE BENGAL AND HIPPURIC ACID TESTS IN PATIENTS WITHOUT OBSTRUCTIVE JAUNDICE OR ACUTE DISEASES OF THE LIVER.

Group.*	No. of tests.	Rose bengal test.		Hippuric acid test (gm.).		
		% 8 min. less than	% 16 min. less than	Min.	Max.	Av.
A . . .	11	61	41	2.00	5.35	4.47
B . . .	10	61-70	41-50	0.33	4.76	3.11
C . . .	10	71-80	51-60	0.54	4.88	2.55
D . . .	10	over 80	over 60	0.17	4.19	1.57

* The Rose bengal test in Group A is normal, B slightly impaired, C definitely impaired and D markedly impaired.

Regardless of the results of liver function tests, many patients with liver damage may have hypoprothrombinemia. Some of these patients may have a satisfactory elevation of the prothrombin concentration following the administration of vitamin K, while others are completely refractive to vitamin K therapy. The following cases demonstrate the level of the prothrombin concentration in patients with different types of diseases of the liver before and after the administration of vitamin K. A detailed history, careful physical examination and complete laboratory data were obtained in each instance. Only the pertinent positive and negative data are recorded.

Clinical Reports. CASE 1.—W. B., U 56826, white male, aet. 55.

Diagnosis. Acute hepatitis.

History. Present entry February 26, 1940. Nine weeks before entry, the patient noted the onset of increasing fatigue. Five weeks before entry, he suddenly became ill and had a fever of 105° F. The temperature fluctuated around 101° F. for 4 days, and then returned to normal. On the third day of fever, he noted the onset of jaundice, which progressed and reached its peak 10 days before entry to the hospital, and since had been slowly regressing. The stools were colored at all times. His appetite was poor and he had lost 30 pounds weight.

Physical Examination. Obese. Temp. 38.2° C (rectal). Pulse 78. Blood pressure 128/90. Skin and sclerae deeply icteric. Abdominal examination negative.

Laboratory Examination.

	Date.	2/26/40.	3/1/40.	3/4/40.	3/11/40.
Bleeding time (min.)		2½	3½	4	1½
Coagulation time (min.)		6½	8	6½	9
Prothrombin concentration (%)		120	70	75	70
Clot retraction index		43	50	43	45
Platelet count (per c.mm.)		580,000	530,000	540,000	610,000
Fibrinogen concentration (%)		1.25	2.21	1.21	0.85
Icterus index		88	72	43	27
Hippuric acid test (gm.)		2.57	2.84	5.41	5.90

Capillary fragility: normal throughout the period of observation.

Blood: Hgb. 105%, erythrocytes 4,900,000, leukocytes 9200. Diff. count: neutrophils 65% (fil. 60%, non-fil. 5%), eosinophils 2%, L., 30%, Mono. 3%.

Urine: bile + + + +, urobilin +1:80, urobilinogen +1:60.

Stool: bile and urobilin present.

Kolmer and Kahn tests: negative.

Course. The patient was completely asymptomatic, except for weakness, during the course of his illness. His temperature varied between 39.5° to 41° C. from February 28 to March 3, 1940, following which time it gradually returned to normal. At the height of the febrile period, a slight drop in the prothrombin concentration occurred. When the temperature returned to normal, the icterus index fell, the fibrinogen concentration decreased and the results of the hippuric acid test returned to normal. The slightly diminished prothrombin concentration persisted throughout the period of observation.

CASE 2.—C. B., U 39230, white male, aet. 62.

Diagnosis. Acute yellow atrophy of the liver.

History. Present entry February 8, 1940. An appendectomy done 1 month previously was followed by an uneventful postoperative course. Urinalysis at that time revealed urobilin positive 1:40, urobilinogen positive 1:40. The rose bengal liver function test on October 14, 1939, revealed 72% retention of the dye in 8 minutes, and 46% retention of the dye in 16 minutes. Ten days before the present entry the patient observed the onset of gradually deepening jaundice, associated with nausea, vomiting and muscular twitchings. He became drowsy, stuporous, and was in coma on entry to the hospital.

Physical Examination. Temperature 36.4° C. Skin and sclerae intensely icteric. Fine muscular contractions in the extremities. Respirations shallow. Liver and spleen not palpable.

Laboratory Examinations.

	Date:	2/9/40.	2/10/40. 10 A.M.*	2/10/40. 6 P.M.
Bleeding time (min.)		6½		
Coagulation time (min.)		7	7½	6½
Prothrombin concentration (%)		20	20	20
Clot retraction index		39	43	41

* 50 mg. phthiocol given intravenously.

Blood: Hgb. 101%, erythrocytes 5,200,000, leukocytes 20,500. Diff. count: neutrophils 85% (fil. 75%, non-fil. 10%), L. 5%, Mono. 5%, metamyelocytes 3.3%, myelocytes 1.7%. Erythrocytes and platelets normal.

Urine: bile + + + +, urobilin negative, urobilinogen negative.

Icterus index: 200.

Van den Bergh: positive immediate direct.

Non-protein nitrogen: 45.5 mg. per 100 cc. (February 9, 1940); 58.8 mg. per 100 cc. (Feb. 10, 1940).

Kolmer and Kahn tests: negative.

Course. Patient failed rapidly and died on the morning of February 11, 1940. Autopsy showed acute yellow atrophy of the liver.

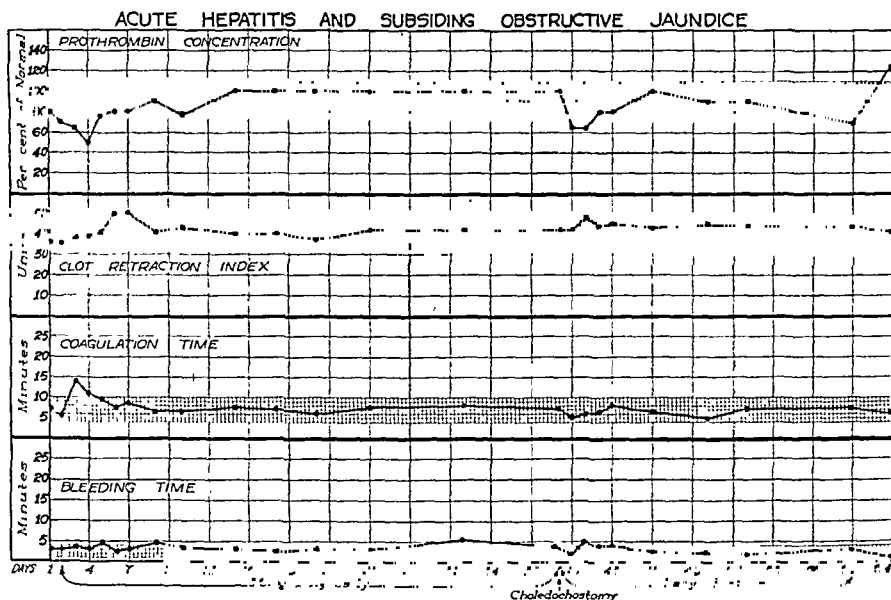


FIG. 3.—The results of hemostatic tests in Case 3.

CASE 3.—A. M., SFH D218246, female, aet. 55.

Diagnosis. Chronic cholecystitis, choledocholithiasis, cholangitis, acute hepatitis, and cholecysto-duodenal fistula.

History. Present entry December 16, 1939. For the past 6 years the patient suffered from recurrent attacks of right upper abdominal pain, sometimes accompanied by slight icterus and gaseous distention. She avoided fatty foods because of nausea. The present attack began 2 days before entry with a sudden severe pain in the epigastrium and right upper quadrant, which radiated to the interscapular region. She became nauseated and vomited. Jaundice was present for 1 day.

Physical Examination. Sclerae and skin slightly icteric. Abdomen markedly distended and painful. Generalized abdominal tenderness, more marked on the left. Marked tenderness, rigidity and rebound tenderness in the right upper quadrant. Tenderness in both costo-vertebral angles.

Laboratory Examinations. Bleeding and clotting tests: Figure 3.

Blood: Hgb. 84%, erythrocytes 4,500,000, leukocytes 14,000. Diff. count: neutrophils 90%, L. 10%.

Urine: bile + + + +, urobilin +.

Stool: colorless, urobilinogen +, bile negative.

Hippuric acid test: 1 gm.

Icterus index:	12/16/39	46	1/ 2/40	19
	12/18/39	75	1/ 8/40	17.5
	12/21/39	79	1/17/40	10.7
	12/26/39	24.5		

Intravenous cholecystograms revealed a non-filling gall bladder. No evidence of stones.

Kolmer and Kahn tests: negative.

Course. There was an intermittent fever to 102° F. until December 19, 1939, when the patient had a chill, followed by a fever of 104° F. The temperature remained elevated to 104° F. for 3 days, then gradually returned to normal during the following 10 days, and remained normal throughout the remainder of her course, except for a slight elevation during the first 9 days after operation. The jaundice increased markedly during the first week, then gradually regressed until it was barely detectable at the time of operation. On January 26, 1940, choledocholithotomy was done under nitrous oxide, oxygen and ether anesthesia. At operation a cholecysto-duodenal fistula was found. A stone was impacted in the common bile duct just distal to the entrance of the cystic duct. The liver was mottled by small areas of brownish-yellow discoloration. The common bile duct was drained for 22 days following surgery. An infection with non-hemolytic *Staph. albus* and *B. proteus* developed around the drain on the sixth day and persisted until the nineteenth day. Otherwise the postoperative course was uneventful. The right rectus wound healed *per primam*. The jaundice cleared rapidly after operation. Transfusions of 500 cc. of citrated blood were given on December 20, December 26, 1939 and January 30, 1940.

The prothrombin concentration was moderately diminished during the course of the cholangitis and acute hepatitis, immediately following operation, and after prolonged drainage of the common bile duct. In the intervals between these periods the prothrombin concentration was normal. Vitamin K₃ was administered from the second day following onset of the acute hepatitis to the day of the operation. After an initial delay, it appeared to be effective in correcting the hypoprothrombinemia of the acute hepatitis. It did not prevent a postoperative diminution in the prothrombin concentration. After drainage of the common bile duct was discontinued, the prothrombin concentration promptly returned to normal.

CASE 4.—M. M., MZH 27926, white female, aet. 65.

Diagnosis. Choledocholithiasis with obstructive jaundice; multiple pyogenic abscesses of the liver.

History. Present entry March 3, 1940. Patient had been a periodic alcoholic for many years. She had remained in good health until 5 days before a previous entry, February 16, 1940, when she experienced vomiting and a dull aching pain in the upper abdomen, associated with light-colored stools, dark urine and slight jaundice. At that time her abdomen was rigid and there was localized tenderness in the right upper quadrant. The heart was enlarged and there was a loud scratching systolic murmur at the mitral area. Blood pressure 110/80. There were scattered râles over the lung fields. Laboratory data at that time revealed:

Blood: Hgb. 83% (12.8 gm.), erythrocytes 4,570,000, leukocytes 18,000. Diff. count: neutrophils 93% (fil. 47%, non-fil. 46%), Mono. 7%.

Icterus index: 32.

The pain rapidly subsided 2 days later, and the patient left the hospital against the advice of her physician. She became more icteric, but the stools were never acholic. She had periods of intermittent fever to 102.6° F. Her only complaint was pain in the chest when rolling on the right side. On the afternoon of March 3, 1940, she had slight epistaxis due to bleeding from the excoriated tip of a spur on the nasal septum. The nose was

packed and the bleeding ceased. It recurred the same evening and the nose was repacked. Early the following morning she had the onset of severe epistaxis. The nose was repacked, but the bleeding continued. She entered the hospital in a moribund condition. At no time during her illness had there been any other evidence of a bleeding tendency.

Laboratory Examinations.

	Date:	3/4/40. 9 A.M.*	3/4/40. 5 P.M.	3/5/40. 9 A.M.
Bleeding time (min.)		7½	1	1
Coagulation time (min.)		18	6½	4½
Prothrombin concentration (%)		3	30	75
Clot retraction index		31	43	41
Plasma fibrinogen (%)		0.87	..	1.01

* 5 mg. vitamin K_s given intravenously.

Capillary fragility: normal.

Platelet count (per c.mm.): 380,000.

Blood: Hgb. 80% = 11.6 gm., erythrocytes 3,700,000.

Urine: sugar + + + +, bile + +.

Icterus index: 75.

The patient was given 5 mg. vitamin K_s intravenously. Several hours later the bleeding stopped, the nasal packs were removed, and no further bleeding occurred. She expired the following morning. The autopsy revealed a stone in the common bile duct and multiple pyogenic abscesses (*E. coli* and *Cl. Welchii*) of the liver, with perforation through the diaphragm into the right pleural cavity. Eight hours after the intravenous administration of 5 mg. vitamin K_s, the bleeding and clotting times were normal, the clot retraction improved, and the prothrombin concentration was elevated to 30%. Twenty-four hours later the prothrombin concentration was 75%. This is an example of a satisfactory response to vitamin K therapy in a patient with severe liver damage.

CASE 5.—A. M., MZH 28140, white female, aet. 52.

Diagnosis. Carcinoma of the head of the pancreas with extensive metastatic invasion of bile ducts, inferior vena cava and the liver.

History. Present entry March 26, 1940. In November, 1939, the patient began to lose weight and strength and complained of constipation, extreme nausea and vague epigastric distress. By January, 1940, she had lost 22 pounds in weight. At that time a complete roentgenologic examination of the gastro-intestinal tract revealed no abnormalities. Cholecystograms revealed a sluggishly functioning gall bladder. The white blood cell count was persistently elevated (14,000 to 20,000 per c.mm.). In January, 1940, she developed edema of both legs and 10 days before entry to the hospital she had the onset of a progressively deepening jaundice.

Physical Examination. Cachectic woman. Skin and scleræ markedly icteric. Heart enlarged 2 cm. to left of mid-clavicular line. Blood pressure 150/100. Lungs clear. Abdomen: small amount of fluid present; marked collateral circulation, with direction of flow upward; liver enlarged, hard and slightly irregular, 8 cm. below right costal margin. Pitting edema of the legs.

Laboratory Examinations. Bleeding and clotting tests: Figure 4.

Capillary fragility: normal.

Blood: Hgb. 72%, erythrocytes 3,710,000, platelets 600,000, leukocytes 18,500. Diff. count: neutrophils 93% (fil. 40%, non-fil. 53%), eosinophils 1%, L., 4%, Mono. 2%.

Urine: bile + + + +, urobilin negative, urobilinogen negative.

Stool: bile negative, urobilin negative, occult blood negative.

Icterus index: 100.

Hippuric acid test: 3.81 gm. (March 28, 1940), 0.5 gm. (April 2, 1940).

Course. The patient failed rapidly and died on April 8, 1940. An autopsy revealed carcinoma of the head of the pancreas with extensive metastatic invasion of the bile ducts, inferior vena cava and liver. This case demonstrates a limited elevation of the prothrombin concentration following the administration of vitamin K. This may be encountered in some patients with extensive destruction of liver parenchyma. A persistently prolonged bleeding time in the presence of only a moderate reduction in the prothrombin concentration is to be noted.

OBSTRUCTIVE JAUNDICE AND METASTATIC CARCINOMA OF THE LIVER.

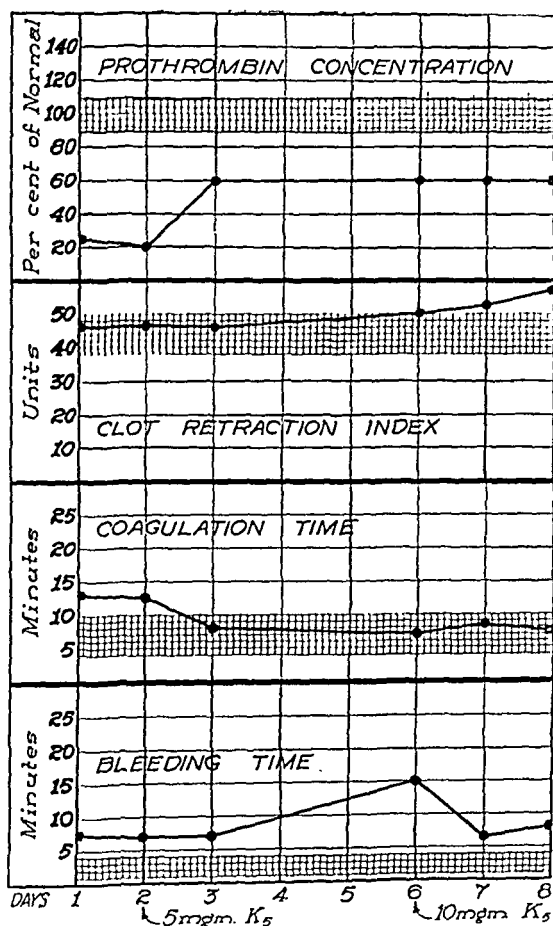


FIG. 4.—The results of hemostatic tests in Case 5.

CASE 6.—C. G., U 54524, white male, aet. 63.

Diagnosis. Portal cirrhosis of the liver.

History. Present entry January 11, 1940. The patient had been a heavy drinker of alcoholic beverages during the greater part of his life, and during recent years had consumed approximately 1 gallon of wine daily. Four years before entry, he was found to have diabetes mellitus. For several months he complained of gas, bloating, belching, flatus, and had 3 to 4 watery stools daily. Three weeks before entry his abdomen became enlarged, his ankles swollen, and his urine dark in color. Much fluid had been removed from his abdomen before hospitalization.

Physical Examination. Skin and scleræ slightly icteric. Brownish pigmentation of hands, arms, head and neck. Liver dullness to fourth right intercostal space anteriorly. Abdomen markedly distended with fluid. Moderate infection about 2 of the 5 paracentesis wounds. Soft pitting edema from the knees to the feet.

Laboratory Examinations.

	Date:	1/11/40.	1/13/40.*	1/14/40.	1/15/40.	1/16/40.
Bleeding time (min.)		4	5½	4½	4	5
Coagulation time (min.)		8	9	6	7½	8
Prothrombin concentration (%) .		55	60	60	60	60
Clot retraction index		38	41	41	34	31

* 30 mg. vitamin K₁ intravenously.

Blood: Hgb. 85%, erythrocytes 4,200,000, leukocytes 3,600. Diff. count: neutrophils 71% (fil. 65%, non-fil. 6%), eosinophils 5%, L. 18%, Mono. 6%.

Urine: green reduction of Benedict's solution, urobilin +1:20, urobilinogen +1:20, bile negative, sediment negative for pigment after potassium ferrocyanide treatment.

Stool: grossly bloody, urobilin +, neutral fat +.

Icterus index: 18.

Rose bengal test: 68% retention of dye in 8 minutes; 58% retention of dye in 16 minutes.

Hippuric acid test: 2.15 gm.

Kolmer and Kahn tests: negative.

Course. On January 13, 1940, 5700 cc. clear straw-colored fluid was removed by abdominal paracentesis. The liver was found to be enlarged 4 cm. below the right costal margin. The spleen was barely palpable. The prothrombin concentration was not altered by the administration of 30 mg. of vitamin K₁. The clinical course was unchanged during the period of observation.

CASE 7. N. N., U 19628, Japanese male, aet. 38.

Diagnosis. Primary carcinoma of liver (cholangioma).

History. Present entry February 21, 1940. For many years the patient had consumed large quantities of alcoholic beverages. He lived in Japan until aet. 16. At aet. 19, he was ill for 1 month with abdominal pain, vomiting, fever and jaundice. He recovered and remained well until March, 1936, when he gradually developed weakness and severe epigastric pain, radiating to the right subscapular region and shoulder. The liver was tender, firm and enlarged 4 cm. below the right costal margin. *E. histolytica* were found in the stools. The patient was given emetine hydrochloride, 1 gr., hypodermically daily for 10 days. On the seventh day he became afebrile. He was subsequently treated with carbarsone and vioform. *E. histolytica* could no longer be found in the stools. Although the jaundice cleared, the liver remained enlarged. The patient recovered, felt well, and returned to work. In August, 1937, he experienced chills, epigastric pain radiating to the right subscapular area, weakness, and recurrent attacks of fever. The liver was hard and irregular, and was enlarged 4 cm. below the right costal margin. Amœbæ were not found in the stools. Sigmoidoscopic and roentgenologic examinations of the gastrointestinal tract were negative. The icterus index was 7. Urobilinogen was present in 1:30 dilution in the urine. The patient recovered under symptomatic treatment and felt well except for an occasional sensation of fullness in the epigastrium. Repeated physical examinations were negative except for enlargement of the liver. In January, 1940, there was a recurrence of fever, chills, weakness, and epigastric pain radiating to the right subscapular region. He entered the hospital 6 weeks after onset of this attack.

Physical Examination. Poorly nourished Japanese male complaining of severe epigastric pain. Temp. 38.6° C. Skin and scleræ icteric. Abdomen: marked collateral venous circulation with direction of flow upward; fluid wave and shifting dullness present; impossible to palpate liver because of rigidity and tenderness in the upper abdomen; large irregular mass in the epigastrium apparently connected to the liver.

Laboratory Examinations.

	Date:	2/25/40.	2/26/40.*	2/27/40.	2/28/40.
Bleeding time (min.)		6	6½	7	6½
Coagulation time (min.)		10½	10	8	6½
Prothrombin concentration (%)		30	30	50	45
Clot retraction index		31	30	32	34

* 10 mg. vitamin K_s intravenously.

Capillary fragility: moderately increased.

Blood: Hgb. 82%, erythrocytes 4,050,000, platelets 190,000, leukocytes 15,600. Diff. count: neutrophils 88% (fil. 70%, non-fil. 18%), L. 10%, Mono. 2%.

Stool: occult blood negative, ova and parasites negative.

Icterus index: 75.

Rose bengal test: 86% retention of the dye in 8 minutes, 81% in 16 minutes.

Plasma fibrinogen: 1.21%.

Plasma ascorbic acid: 0.19 mg. per 100 cc.

Kolmer and Kahn tests: negative.

Course. Roentgen examination revealed a markedly enlarged liver, pressure deformity of the duodenum due to a large mass in the epigastrium, and marked thickening of the pleura in the right lower chest. On February 26 the patient developed oliguria, coma and involuntary muscular contractions. The N.P.N. was elevated to 109 mg. per 100 cc. He expired on February 28, 1940. At autopsy he was found to have had chronic cholecystitis, large intrahepatic stones, and a primary carcinoma of the liver, originating in the bile ducts.

The bleeding time was slightly prolonged and the clotting time at the upper limits of normal. The prothrombin concentration was low and the clot retraction poor. There was a slightly increased capillary fragility, which was probably due to vitamin C deficiency. The platelet count was moderately low. Following the intravenous administration of 10 mg. vitamin K_s, there was a slight shortening of the clotting time, and a slight elevation of the prothrombin concentration. The bleeding time and clot retraction index were not significantly altered.

Comment. No significant correlation was found to exist between the results of the oral hippuric acid liver function test and the prothrombin concentration, either before or after the administration of vitamin K. Patients with evidence of severely impaired liver function were found to have normal prothrombin concentrations, low prothrombin concentrations which could be elevated to normal following the administration of vitamin K, or hypoprothrombinemia, which was completely refractive to vitamin K therapy.

We have found that in acute diseases of the liver, such as hepatitis, or acute yellow atrophy, that the prothrombin concentration may be normal or markedly diminished, and that fluctuations in its level appear to be conditioned by the severity of the illness, and that the responses, if any, to the administration of vitamin K are usually

delayed. When there is chronic diffuse liver damage such as occurs in portal cirrhosis, there may be a low prothrombin concentration which is usually refractive to the administration of vitamin K. Extensive destruction of liver parenchyma by infection or by primary or metastatic carcinoma is usually accompanied by a low prothrombin concentration, which may be moderately elevated following the administration of vitamin K. In obstructive jaundice, the prothrombin concentration may be diminished, depending upon the degree and duration of the obstruction, and upon the type and extent of the concomitant liver damage, and following the administration of vitamin K, it is usually elevated to normal. When obstructive jaundice is complicated by extensive destruction of liver tissue, the response to vitamin K may be limited.

A question of great interest at the present time is whether the prothrombin concentration can be used as a liver function test, provided that an adequate supply of vitamin K is available for the liver. In general, when one function of the liver is impaired, there is usually some disturbance of all other functions. The exceptions to this rule are so numerous, however, that no single liver function test can be said to measure the total functional capacity of the liver. Reduction of the prothrombin concentration under certain circumstances, may, and under others may not parallel alterations of the known functions of the liver. If the following assumptions can be made: 1, that prothrombin is manufactured exclusively by the liver; 2, that our present indirect methods actually measure prothrombin; 3, that vitamin K is the only dietary substance concerned in the manufacture of prothrombin; and 4, that prothrombin must not be utilized, destroyed, or inactivated except by catabolic processes progressing at a constant rate; then the prothrombin concentration after adequate administration of vitamin K would appear to be a measure of the ability of the liver to produce prothrombin.

Summary. 1. No significant correlation was found between the results of the hippuric acid liver function test and the plasma prothrombin concentration in various diseases either before or after the administration of vitamin K.

2. Patients with severe impairment of liver function as demonstrated by the hippuric acid test may, at the same time, have a normal prothrombin concentration.

3. Plasma prothrombin concentration may be elevated to normal following the administration of vitamin K, despite markedly impaired liver function as shown by the hippuric acid test.

4. Failure to recover from hypoprothrombinemia following the administration of vitamin K cannot be correlated with the degree of impaired liver function as shown by the hippuric acid test.

5. Regardless of the results of liver function tests, it has been found that: (a) In acute diseases of the liver such as acute hepatitis and acute yellow atrophy, the fluctuations in the prothrombin con-

centration are conditioned by the severity of the illness and are not ordinarily influenced by the administration of vitamin K. (b) In chronic diffuse diseases of the liver, such as portal cirrhosis, there may be a low prothrombin concentration which is usually not elevated following the administration of vitamin K. (c) In obstructive jaundice, there may be a low prothrombin concentration which usually can be significantly elevated by the administration of vitamin K. When obstructive jaundice is complicated by severe liver damage, the response to vitamin K may be limited.

The authors are greatly indebted to Dr. William J. Kerr for permission to use the data in Case 2, to Dr. T. L. Althausen for the data in Case 6, and to Dr. F. I. Harris and the staff of the Mt. Zion Hospital for many courtesies and for permission to use the data in Cases 4 and 5.

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SOME BACTERIOLOGIC OBSERVATIONS ON PNEUMONIA.

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DURING the past 5 years we have instituted a bacteriologic procedure in the study of pneumonia which, although incomplete, yields us data that aid in the analysis of individual cases and series

of cases. This paper deals with a statistical analysis of the variations in bacteriology of the pneumonias at Mercy Hospital from July, 1935, to June, 1940.

We have thought it best to include the months of July 1 to June 30 of the following year as representing each pneumonia year, although in one of the tables the years are further subdivided into 6-month periods to bring out further details.

Each pneumonia patient on admission has blood drawn for culture. One cubic centimeter of the blood is mixed with 15 cc. of hormone veal agar, buffered at pH 7.2, and a poured plate made. Ten cubic centimeters of blood are cultured in 100 cc. of hormone veal broth buffered at pH 7.2. Blood culture is repeated daily on all patients until there is definite clinical improvement. Sputum is obtained as soon as possible after admission. The analysis includes a direct microserologic test for the type of *Dip. pneumoniae* (Neufeld reaction); direct smears stained by Gram and Ziehl-Neelsen's methods; mouse inoculation; and culture on blood agar to identify the various types of bacteria present. The mouse inoculation not only verifies the type of *Dip. pneumoniae*, but also aids in isolating *H. influenzae*, which we have found often grows well in the peritoneal cavity in conjunction with *Dip. pneumoniae*.

If the specimen of sputum is unsatisfactory, or if the course of the pneumonia is unusually prolonged, a second or third specimen is secured. If the patient produces no sputum within the first 12 hours after admission, a pharyngeal swab is secured for preliminary study.

During the last 2 years of the study, identification and classification of all organisms have been made according to Bergey's Manual of Determinative Bacteriology. Previous to that time the streptococci were classified only by the type of hemolysis. We have not used the Lancefield grouping on the streptococci in this series. Dr. Maud Menten at the Children's Hospital in Pittsburgh has found that about 90% of the beta-hemolytic streptococci isolated from the upper respiratory tract in children during this period belong to Lancefield group A.³ The staphylococci which will be mentioned in the paper are all *Staphylococcus aureus*, coagulase positive, and the great majority are hemolytic. Micrococci and other species of staphylococci have been excluded. No particular attention has been paid to any of the other microorganisms of the respiratory tract except *H. influenzae* and *Klebs. pneumoniae*. We have isolated various species of *Klebsiella* from sputum and once from the lung and blood at autopsy (*Klebs. ozaenae*). Since none of these was *Klebs. pneumoniae*, and because in none of the cases was there sufficient justification clinically or pathologically to call it a Friedlander's pneumonia, we have not included this microorganism in our analysis.

The series includes 842 consecutive cases of adult pneumonia (over 15 years of age) admitted to the hospital from July 1, 1935, to

TABLE 1.—GENERAL STATISTICS.

Year.	Mean age.	Total.		Cases with adequate bacteriology.		Results of blood cultures.	
		Cases.	Deaths.	Total.	<i>Dip. pneumoniae</i> isolated.	Total.	<i>Dip. pneumoniae</i> isolated.
1935-1936	42	122	46 (38%)	111	111 (100%)	121	38 (31%)
1936-1937	40	179	79 (44%)	158	151 (96%)	175	63 (36%)
1937-1938	40	192	72 (37%)	187	181 (97%)	189	55 (29%)
1938-1939	44	158	63 (40%)	156	145 (93%)	152	50 (33%)
1939-1940	51	191	60 (31%)	174	151 (87%)	180	44 (24%)
Total	..	842	320 (38%)	786	739 (94%)	817	250 (31%)

TABLE 2.—ANALYSIS OF DIP. PNEUMONIÆ TYPES.

Types.	1935-1936.		1936-1937.		1937-1938.		1938-1939.		1939-1940.		Total.	
	Cases.	%.	Cases.	%.	Cases.	%.	Cases.	%.	Cases.	%.	Cases.	%.
I	17	15	25	17	20	11	17	12	19	13	98	13
II	14	13	33	22	60	32	27	19	16	11	150	22
III	17	15	22	15	17	9	24	17	30	20	110	15
IV	4	4	5	3	4	2	13	9	5	3	31	4
V	1		9	6	9	5	9	6	6	4	34	5
VI	1		1		1		..		3	2	6	1
VII	8	7	7	5	8	4	10	7	15	10	48	6
VIII	9	8	8	5	6	3	12	8	17	11	52	7
IX	3	3	2		2		1		4	3	12	
X	5	5	4	3	3	2	2		1		15	
XI	3	3	1		2		1		2		9	
XII	1		3	2	2		4	3	3	2	13	
XIII	1		1		2		1		..		5	
XIV	2		1		..		2		3	2	8	
XV		1		1		..		2	
XVI		3	2	3	2	..		6	
XVII		1		1		1		1		4	
XVIII	2		..		2		2		3	2	9	
XIX		1		..		2		1		4	
XX	5	5	2		1		2		1		11	
XXI	
XXII		1		2		..		3	
XXIII		1			1	
XXIV		1			1		2	
XXV	6	5	2		2		3	2	1		14	
XXVI	1			1	
XXVII	1		2		..		1		..		4	
XXVIII	1		2		3	2	..		2		8	
XXIX		2		1		2		2		7	
XXXI		1			2		3	
XXXII		3	2	..		1		4	
Not types I to XXXII	9	8	14	9	23	13	1		8	5	55	7
Multiple types*		4		2		4		10	

* Eighteen patients who had more than one type in various specimens are placed in the group which corresponded with the type of *Dip. pneumoniae* found either in the blood or in the lung at autopsy.

June 30, 1940. The cases were proved to be pneumonia by Roentgen ray or autopsy, the latter in the small group of postoperative pneumonias, where clinical, bacteriologic and Roentgen ray study were deemed inadequate for accurate diagnosis in many cases. No effort has been made in this paper to separate specifically treated from untreated cases.

Table 1 shows general statistics for the 5 years. The column labelled "Cases with Adequate Bacteriology" included cases who had either sputum and blood culture analyses, or bacteriologic study of autopsy material.

In Table 2, which shows the type incidence of *Dip. pneumoniae*, it will be noticed that the yearly incidence of Types I, III, V, VII and VIII has been fairly constant. On the other hand, there has been a marked variation in incidence of Type II. This variation follows a curve which reaches its peak in the year 1937-1938. It suggests an epidemic due to Type II during the period studied. The increase in incidence of Type III in the year 1939-1940 may possibly be accounted for by the fact that the mean age for this group is higher than that of any other year (Table 1).

TABLE 3.—*DIP. PNEUMONIAE* BACTEREMIA. JULY, 1935, TO JUNE, 1940.

Type.	Total cases.	<i>Dip. pneumoniae</i> bacteremia.	
		Cases.	%.
I	98	31	31.6
II	150	91	60.7
III	110	37	33.6
IV	31	10	32.3
V	34	13	38.3
VI	6	2	
VII	48	11	23.0
VIII	52	18	34.6
IX	12	4	
X	15	3	20.0
XII	13	5	
XIV	8	2	
XVI	6	1	
XVIII	9	4	
XX	11	4	
XXII	3	1	
XXV	14	9	
XXVI	1	1	
XXXII	4	2	
Not Types I to XXXII	55	3	

Table 3 illustrates the per cent invasiveness of the various types of *Dip. pneumoniae*, as determined by the incidence of pneumococci bacteremia. An outstanding point to be noted here is the very high degree of invasiveness of Type II. There is no great variation in the invasiveness of any type from year to year, except in 1939-1940 when the percentage of bacteremias of Type II dropped to 40.

The occurrence of more than one type of *Dip. pneumoniae* in a single specimen of sputum was found in a few cases each year. In the

majority of these the type acting as a causative agent in the pneumonia could be determined by repeated sputum examinations or blood culture. Lung puncture has not been used as a bacteriologic procedure in this series. It is interesting to note here that one case showed *Dip. pneumoniae* Type II on repeated examination of sputum, and Type I in the blood at the same time. Another case having Type I in the sputum had a Type II bacteremia.

Since December, 1936, we have seen clinically a different type of pneumonia than the usual typical croupous infection. The clinical observations have been substantiated by postmortem examinations. This variation from the relatively pure pneumococcic pneumonia was described by us in 1937,² when we used the term post-influenzal pneumonia. It has been noted in other localities, particularly by Reimann⁴ who referred to it as atypical pneumonia. We now think it better to call this a mixed infection pneumonia because of the varied clinical, bacteriologic and pathologic pictures. The mixed infection has been much more common in our district in the past few years than croupous pneumonia. Because virus studies are lacking in our cases we do not know what rôle such infectious agents have played in the disease. However, we accept the fact that they are in all likelihood present in the early stages.

TABLE 4.—INCIDENCE OF STREP. PYOGENES, STAPH. AUREUS AND H. INFLUENZÆ.

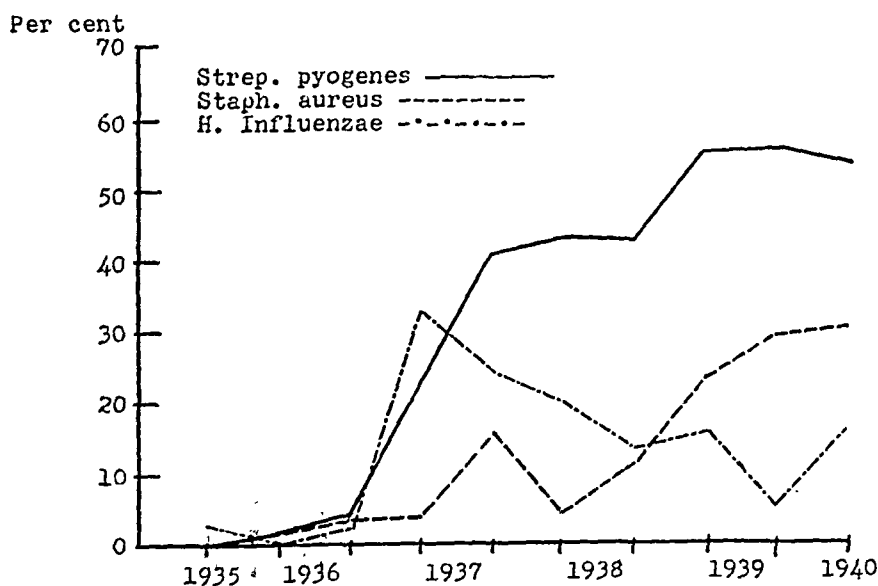


Table 4 shows the relative incidence of *Strep. pyogenes*, *Staph. aureus* and *H. influenzae* isolated from sputum, blood or lung at autopsy in pneumonias. The graph illustrates the variation in occurrence of these organisms during the 5 years. It is interesting that during the period when *H. Influenzæ* was frequently found, the

cases developing meningo-encephalitis occurred and several autopsies revealed Zenker's degeneration of recti muscles. Also, since January, 1939, when there was an increase in the percentage of cases showing *Staph. aureus*, multiple lung abscesses have been a frequent finding at autopsy.

Strep. pyogenes was found in the blood during life in 6 cases, and in 1 of these *Dip. pneumoniae* was present in the blood at the same time. These 6 cases occurred at scattered periods during the 5 years. *Staph. aureus* was present in the blood in 21 cases and all but 2 of these occurred from January, 1939, to June, 1940. *H. influenzae* was never isolated from the blood, either during life or at autopsy. Many of the cases with streptococcic or staphylococcic bacteremia had two or more consecutive daily positive blood cultures.

TABLE 5.—ANALYSIS OF MOST COMMON COMPLICATIONS. JULY, 1935 TO JUNE, 1940.

Lesion.	Cases.	Microorganism found in lesion.		
		<i>Dip. pneumoniae.</i>	<i>Strep. pyogenes.</i>	<i>Staph. aureus.</i>
Empyema	34	24	6	4
Acute meningitis	4	4		
Acute endocarditis	6	4	..	2
Acute pericarditis	4	1	3	
Multiple abscesses of lung	21	8	4	9
Pleural effusion (sterile)	22			
Acute meningoencephalitis (sterile)	13			
Delayed resolution	133			

Table 5 is shown primarily to list the causative organisms in the main complications which have occurred. Many of the bacteriologic findings are from cultures of autopsy material. It is noteworthy that all the cases of pleural effusion and meningo-encephalitis occurred from July, 1937, to June, 1940, and as we have mentioned above, the majority of the cases of multiple lung abscesses have occurred since January, 1939. For purposes of comparison we have included in the list of delayed resolution all cases who ultimately recovered without other complications, who had fever and clinical signs lasting longer than 12 days. There was a gradual increase in incidence of this complication over the 5-year period, the number of cases being 5, 16, 25, 36 and 51, respectively. It may be possible that some of these cases had developed multiple lung abscesses, but proof of this is lacking.

The bacteriology of autopsy material has borne out the findings during life. Table 6 gives the frequency of the four microorganisms isolated from the lung at autopsy. The cases have been separated into the two main pathologic groups to demonstrate the fact that the microorganisms other than *Dip. pneumoniae* occurred much more frequently in the mixed infection group than in the lobar or bronchopneumonias. Few of the autopsies performed on pneumonias in

the period from July, 1935, to January, 1937, were of the post-influenzal or mixed infection types pathologically.

TABLE 6.—BACTERIOLOGIC DATA FROM AUTOPSY MATERIAL.
JANUARY, 1937, TO JUNE, 1940.

Microorganism isolated.	Lobar pneumonia or bronchopneumonia.		Post-influenzal or mixed infection pneumonia.	
	Cases.	%.	Cases.	%.
<i>Dip. pneumoniae</i>	31	64.6	22	59.5
<i>Strep. pyogenes</i>	7	14.5	13	35.2
<i>Staph. aureus</i>	11	23.0	23	62.2
<i>H. influenzae</i>	2	4.2	11	29.8
Total No. cases	48		37	

It may be appropriate here to outline the most characteristic pathologic findings in the postinfluenzal or mixed infection pneumonias. Influenza, as has been described a number of times in the past, is characterized by an ulcerative tracheitis, bronchitis and bronchiolitis without alveolar exudate, and is in all likelihood a virus disease from which *H. influenzae* may also be isolated. When secondary infection due to any of the bacteria of the respiratory tract (most commonly *Dip. pneumoniae*, *Strep. pyogenes* or *Staph. aureus*) is superimposed, a serous, hemorrhagic or purulent pneumonia results, and may be characterized by interstitial pneumonitis, infected thromboses of pulmonary blood-vessels, and multiple lung abscesses.¹ It is of course possible to find all gradations of involvement in a lobular pneumonia which may advance to form a coalescing pneumonia that is lobar in distribution.

We have found it difficult to separate the pneumonias into distinct groups: pure pneumococcic pneumonia and mixed infection pneumonia. It must also be remembered that pure streptococcic or staphylococcic pneumonia occur. In the group of lobar pneumonias shown in Table 6 there were 2 cases from which all cultures yielded pure growths of *Strep. pyogenes*; and 1 lobar and 1 bronchopneumonia in this group were pure *Staph. aureus* infections. Isolation of *Strep. pyogenes*, *Staph. aureus* or *H. influenzae* in addition to the pneumococcus, whether from clinical or postmortem material, must be considered with reserve, until there is some confirmatory evidence of mixed infection. Any of the microorganisms which may be responsible for the pneumonia may also be present in the respiratory tract without acting in the infection.

Conclusions. 1. During the 5 years from July, 1935, to June, 1940, there has been a marked variation in the bacteriology of pneumonia patients in this series.

2. In addition to *Dip. pneumoniae*, *Strep. pyogenes*, *Staph. aureus* and *H. Influenzae* have appeared to play a major rôle in pneumonia in this district.

3. *Dip. pneumoniae* Type II has varied greatly in incidence during this period, and assumed almost epidemic proportions in 1937-1938.

4. *Dip. pneumoniae* Type II has shown greater invasiveness of the blood than any other type.

The author wishes to express his thanks to Drs. W. W. G. MacLachlan and H. H. Permar for their advice in the preparation of this paper.

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VITAMIN E IN THE TREATMENT OF FIBROSITIS.*

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EVANS and Burr⁴ were the first investigators to describe a spastic paralysis occurring in the suckling young of rats when the mothers are deprived of vitamin E. At 21 days these sucklings begin to show difficulty in regaining their limbs when placed on their backs. The disease increases in severity during the ensuing 4 to 5 days and by the twenty-fifth day of life practically all the animals destined to develop the disease will exhibit it. About 35% of the affected animals die, 17% recover completely, and 48% continue to exhibit paralysis of some limb or body group of muscle throughout life. There are marked variations in these results. All attempts to cure the disease after it has been established for several days fails. However, the disease is prevented if the mother's diet is shifted from a vitamin E deficient diet to one rich in vitamin E on the day of birth of the rats. It is already too late to forestall disaster if the shift to a vitamin E rich diet is delayed until the earliest appearance of paralysis in any member of the litter. Einarson and Ringsted³ have shown that diets deficient in vitamin E will cause similar changes in adult rats. Blumberg,² Madsen,⁵ Morgulis and Spencer,⁶ Morgulis, Wilder and Spencer⁷ have stressed the importance of deficient vitamin E diets causing primary muscular dystrophy.

Three clinicians have recently reported excellent results in the use of vitamin E or the synthetic tocopherols in the treatment of primary muscular dystrophies or of muscular dystrophies resulting from neurologic conditions. Bicknell¹ gave $\frac{1}{2}$ ounce of dried wheat germ to 18 patients with muscular dystrophies. Improvement was noted in 12 cases and no improvement in the remaining 6 cases. The period of treatment varied from 6 weeks to 18 months. The shortest period of treatment in the improved group was 2 months. Wechsler¹⁰ described 2 cases of amyotrophic lateral sclerosis that

* Furnished through the courtesy of E. R. Squibb & Sons.

improved by treatment with a synthetic vitamin E (dl-alpha-tocopherol). Stone⁹ reported excellent clinical improvement in 5 children with muscular dystrophy, 1 child with muscle atrophy following anterior poliomyelitis, and 1 child with muscle atrophy after an attack of multiple neuritis. He employed 2 to 6 cc. of wheat germ daily.

These experiments and clinical reports, particularly those concerning the muscle changes associated with vitamin E deficiency, stimulated the writer to try the clinical effect of vitamin E in the treatment of fibrositis. This condition may be defined as an inflammatory reaction of fibrous connective tissue present anywhere in the body. The pathologic picture found in fibrositis and that described by Pappenheimer⁸ as occurring in ducklings on a deficient vitamin E diet are practically alike except for the new formation of palpable fibrous nodules. Fibrositis may occur as a primary disease or as a secondary disease. Internists are familiar with the muscle pain, swelling and pain associated with atrophic arthritis or gout. They have seen painful swollen bursæ associated with many of the rheumatic diseases. Very few, however, are familiar with the disease as a primary one. Many common diseases are in fact evidences of primary fibrositis but masquerade under various titles. These are variously diagnosed as lumbago, torticollis, muscular rheumatism, tendinitis, periarticular fibrositis, panniculitis, myositis, and so on. A working classification of diseases of the muscles is given below.

- I. PARENCHYMATOUS MYOSITIS. (a) Suppurative. (b) Nonsuppurative.
- II. MYOPATHIES. A. Primary myopathies. 1. A heterogeneous group such as pseudohypertrophic, fascio-scapulo-humeral, bulbar, juvenile scapular, infantile hereditary. 2. Myasthenia gravis. 3. Amyotonia congenita. 4. Myotonia congenita. 5. Myotonia atrophica. B. Progressive nuclear muscular atrophy. 1. Mainly of small muscles of hands. 2. Hereditary, familial, of infancy and childhood. 3. Subacute and chronic poliomyelitis. 4. Progressive bulbar palsy. 5. Chronic progressive ophthalmoplegia.
- III. INTERSTITIAL MYOSITIS. A. Myositis ossificans. B. Intramuscular fibrositis. 1. Primary (muscular rheumatism, lumbago, torticollis, etc.). 2. Secondary (atrophic arthritis, rheumatic fever, gout, etc.).

Wheat germ oil was given in doses ranging from 2 to 8 cc. to 82 patients: 30 cases of primary fibrositis, 20 cases of fibrositis secondary to atrophic arthritis, 20 cases of fibrositis secondary to hypertrophic arthritis, 1 case of fibrositis secondary to gout, 3 cases of sciatica (cause unknown), and 8 neurotic patients. All these cases had been observed for a period of 3 months to 2 years under different methods of therapy such that their clinical status at the time of beginning vitamin E therapy was "stabilized." The wheat germ oil was taken in equally divided doses 3 times daily. The oil was taken in a tablespoon of milk at meal time. Many patients complained of the unpalatable taste, or that the oil repeated. The 2 patients reported in this paper as having taken the vitamin E molecular distillate, that contained 40 mg. of alpha tocopherol in each capsule, noticed no unpleasant taste or other untoward gastric effects.

Thirty cases of primary fibrositis were treated with vitamin E in doses of 2 to 8 cc. daily and all were completely relieved of all symptoms. Two of this group had only mild relief from symptoms after having received 3 cc. of wheat germ daily for 4 weeks. These 2 cases were then given a vitamin E molecular distillate containing 120 mg. of naturally occurring alpha tocopherol daily. They were completely relieved of all symptoms after 1 week of such therapy.

Twenty cases of atrophic arthritis with secondary fibrositis were given 2 to 8 cc. of wheat germ daily over a period of 2 to 4 months. Eight noticed definite improvement in muscle soreness and stiffness. Twelve patients experienced no relief.

Twenty cases of hypertrophic arthritis with secondary fibrositis were given 2 to 6 cc. of wheat germ daily over a period of from 2 to 6 months and none noticed improvement in the soft tissue structures.

One case of gout was given 4 cc. of wheat germ daily for a period of 4 weeks without relief from the extreme muscle soreness.

Three cases of sciatica, cause unknown, were given 4 cc. of wheat germ daily for a period of 4 weeks without relief.

Eight patients diagnosed as psychoneurotics ("psychosomatic rheumatism") were given wheat germ oil over a period of 2 to 3 months without relief. These were all later relieved by the giving of barbiturates or bromides.

Summary. Vitamin E is of value in the treatment of primary fibrositis. Some of the more severe cases may require the more concentrated preparation of vitamin E to obtain a complete result. Vitamin E is of little value in the treatment of secondary fibrositis. These studies tend to indicate that primary fibrositis may be a metabolic rather than an infectious process.

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THE QRS COMPLEX IN PRECORDIAL LEADS IN ANTERIOR WALL INFARCTION. TRUE AND FALSE INFARCTION CURVES.*

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FROM the numerous works that have been published in recent years on the value of precordial leads in clinical electrocardiography

* It has not been possible for the author to see the proof of this manuscript.—
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it is evident that such leads are particularly serviceable for the diagnosis of anterior wall infarction.

Wilson *et al.*¹⁵ described in 1933 the *absence of the initial positive deflection* as a typical change in the *QRS* complex in anterior wall infarction. In the new terminology, which will be employed throughout in the following, this phenomenon is called *absence of the R wave* in the *QRS* complex in precordial leads.

Subsequently, this finding was confirmed by numerous investigators. Some authors^{9,18} found that the absence of *R* in anterior wall infarction is not always complete, and that there may be left a little remnant of the *R* wave in the form of a small initial positive deflection. Other authors¹⁰ emphasize that only the complete absence of *R* is characteristic of anterior wall infarction, although a diminished *R* wave (less than 2 mm.) is suggestive of myocardial degeneration. Bohning and Katz¹ state that a diminished *R* wave indicates coronary sclerosis.

As well as the typical change in the *QRS* complex in anterior wall infarction, some deviating *QRS* changes have been described in the course of time. Thus, in 1934 Wood and Wolferth¹⁷ described W-formed, "bizarre" *QRS* complexes. In 1936 the writer^{11a} showed that in addition to the classical abnormality of the *QRS* complex—complete absence of the *R* wave—there was also a splitting of the remaining negative part of the *QRS* complex in 2 of his 3 cases, and a suggestion of such a splitting in 1 case. Furthermore, a serial examination showed that this splitting during the course of illness may vary in size and finally become so large that an apparently normal *QRS* complex with an apparently normal *R* wave results. It was pointed out, however, that this *QRS* complex differs essentially from the *QRS* complex that was present before the infarction in this respect, that the *R* wave is not an initial positive deflection but is preceded by a little *Q* wave. Langendorf and Pick⁸ in 1938 were able to confirm this finding. In 1936, Faleiro⁵ reported that the *QRS* complex in an apex lead may be normal.

In experimental studies, Wilson *et al.*^{6,13a,b,14a,b} found the classical infarction curves with lacking *R* wave, consisting of a single negative deflection, and also deviating W-shaped *QRS* complexes, in which the individual components were subject to great variability. The first mentioned complexes were found in particular over the central parts of an experimental infarct, while the deviating *QRS* complexes were found over the marginal areas. Kossmann and de la Chapelle⁷ have analyzed 4 cases of anterior wall infarction on this basis, designating the two types of *QRS* complexes respectively as the "central" type and the "marginal" type. Apart from this, the experimental studies of Wilson and collaborators have had but slight effect on subsequent clinical work. Also in the most recent works on the changes in precordial leads in anterior wall infarc-

tion^{2,4,12} the *QRS* changes in typical cases are described as disappearance of the *R* wave.

Author's Studies on the Analysis of the *QRS* Changes in Precordial Leads in Cases of Anterior Wall Infarction. In my own studies on the *QRS* changes in precordial leads in anterior wall infarction these changes are found to be so polymorphous that they can be described only in a few of the cases by absence of the *R* wave or by lack of an initial positive deflection—as is customary in clinical works. The *QRS* complexes that are not characterized sufficiently by this description are so numerous that it really is misleading to designate them as deviations, with the “classical” changes being set up as the rule.

The writer's material of cardiac infarction includes 23 cases of clear-cut anterior wall infarction that will be reported in detail in a subsequent work. In these 23 cases a total of 192 electrocardiograms were taken in 5 leads; in the 3 conventional leads from the extremities and also CF_2 and IVF.*

Figure 1 shows two normal *QRS* complexes (1*a* and 1*b*) in CF_2 and IVF respectively, and different types of *QRS* complexes obtained in some of the writer's cases of anterior wall infarction. *In 20 of these 23 cases the *QRS* complex in CF_2 and IVF represented one of the pathologic types shown in Figure 1, and this phenomenon was observed in all the records, the time relation of which to the acute attack has varied from a few hours to several years.* Of the remaining 3 cases, 2 showed a *QRS* complex of one of the recorded types in CF_2 and IVF respectively. Thus only in 1 case did the tracing show a deviating *QRS* complex in both precordial leads; and this deviation consisted in the presence of an initial positive deflection.

The deviation from the normal *QRS* complexes (1*a* and 1*b*) that characterizes all these apparently widely different *QRS* complexes is *the presence of an initial negative deflection.*

It will be noticed at once that the classical description of the changes in the *QRS* complex in anterior wall infarction as absence of the *R* wave covers only some of the cases. Further, it is seen easily that the expression “absence of initial positive deflection,” as well as the analogous expression “presence of initial negative deflection,” suggested above, is *insufficient* to characterize all the different types of infarction curves.

Classical infarction curves of the type which usually is described as characteristic of anterior wall infarction are shown in Figure 1, 1*c* and 1*d* (Leads IVF and CF_2 respectively). These *QRS* complexes quite correspond to the *QRS* complexes obtained by Wilson *et al.* from the middle of an experimental infarct extending clear through the wall of the ventricle. Such a *QRS* complex is characterized by complete absence of the *R* wave, its upward

* CF_2 : from the fourth left intercostal space just outside the sternal border to the left leg. IVF: from the apex to the left leg.

("preintrinsic") deflection as well as the downward ("intrinsic"), as the prerequisites of such deflections are lacking. So the initial negative deflection has to be looked upon as a fundamentally new deflection, brought about by the infarct, and designated by Wilson *et al.* as a *Q* wave. In analogy to this, the *QRS* complexes shown in Figure 1, 1*c* and 1*d*, may be said to be characterized by the *appearance of an initial negative deflection in connection with a complete abolition of the R wave*. *QRS* complexes of this type are to be characterized as typical central curves.

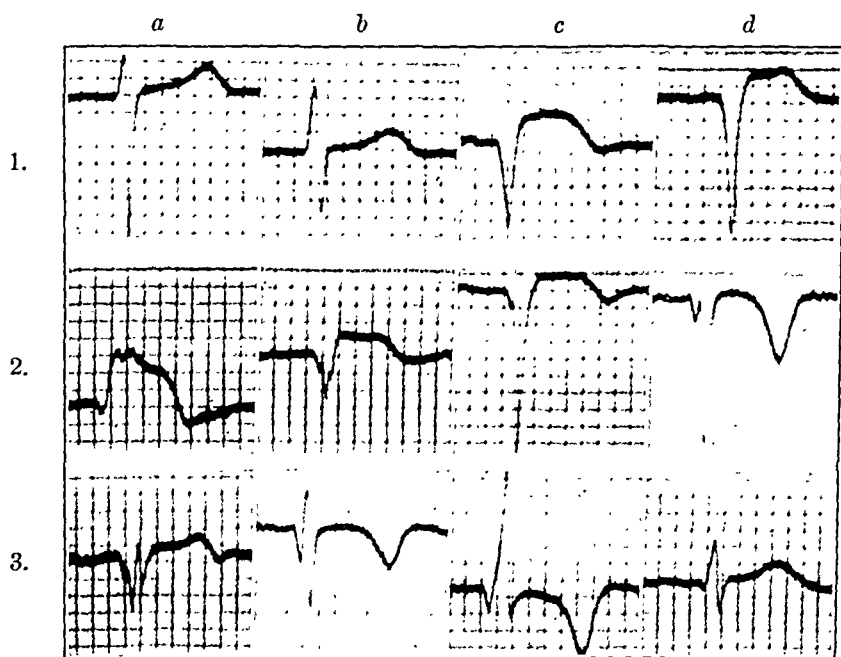


FIG. 1.—(1/1 natural size. 1 mV = 1 cm.) Two normal ventricular complexes (1*a* and 1*b*) and different types of ventricular complexes from the writer's cases of anterior wall infarction.

The *QRS* complex (Lead CF₂) shown in Figure 1, 3*b*, represents a type which corresponds closely to the *QRS* complexes obtained by Wilson *et al.* from the marginal parts of an experimental infarct, or from an infarct extending only through the inner layers of the ventricular wall, which have been called *QRS* complexes of marginal type. Such a *QRS* complex must be interpreted as resulting from a new initial negative deflection preceding the *R* component (*i. e.*, a *Q* wave); this is followed by the "preintrinsic" and "intrinsic" deflections of the *R* wave, the latter of which will usually appear in the form of a steep hair fine line. So this *QRS* complex is characterized by the *appearance of the Q wave and a preserved, possibly reduced, R wave*.

Also the *QRS* complexes shown in Figure 1, 3*a* and 2*d*, are of

marginal type, containing the same components as in the preceding case. These QRS complexes are characterized by the *appearance of an initial negative deflection (a Q component) and a diminution of the R wave*. After the usual conception, in these cases one would say there is a complete absence of the *R* wave and the remaining part of the QRS complex is notched.

Figure 1, 2c shows a QRS complex which greatly resembles the typical central QRS complex in 1d. In the initial descending deflection, however, there is a small but distinct notch—representing the *R* wave—of a similar localization to that of the somewhat greater splitting seen in 2d. So this QRS complex is characterized by the *appearance of an initial negative deflection and almost complete abolition of the R wave*.

The QRS complex in 2b is to be interpreted in a similar manner, even though we here meet with two splittings, so that it is more difficult to determine what parts of the QRS complex correspond to the *R* component.

If the abolition of the *R* wave is even more pronounced, the result may be QRS complexes that differ from typical central curves merely in this respect, that a small node is found on the initial descending deflection, marking the remnant of the *R* component.

The QRS complex in Figure 1, 2a differs from the others, and yet it may be analyzed after the same principles. Thus we find here an initial negative deflection (*Q* wave) followed by the ascending limb of the *R* wave, whereas the descending limb ("intrinsic deflection") is completely absent. This QRS complex is characterized by the *appearance of an initial negative deflection and partial abolition of the R wave* (involving only the "intrinsic deflection").

Finally, Figure 1, 3c and 3d, shows some QRS complexes (both from IVF) which look a great deal like normal QRS complexes. In both cases, however, there is an initial negative deflection (*Q* wave). So these QRS complexes are characterized by the *appearance of an initial negative deflection and a preserved (or possibly diminished) R wave*. In IVF there may normally be a little *Q* wave preceding a large *R* wave. So marginal QRS complexes with a small *Q* component and a large *R* component preserved in Lead IVF cannot by themselves be distinguished from normal QRS complexes; but as a rule they may be recognized through comparison with the QRS complex in CF₂.

From this analysis of the infarction curves shown in Figure 1 it is evident that although they differ greatly in appearance they still have certain fundamental features in common, so that there may be said to be only a difference of degree between the different complexes. Actually there is a quite gradual transition from the classical infarctions, designated as pure central curves (Fig. 1, 1c and 1d), through apparently typical curves with node formations and small

notches (*2b*, *2c* and *2d*) to typical, so-called marginal, *QRS* complexes with a "splitting" so large that it has to be designated as an *R* wave (*3a*, *3b*, *3c* and *3d*).

As is evident from the preceding, all the types of *QRS* complexes here described can be explained in keeping with the same principles, if in accordance with the viewpoints advanced by Wilson *et al.* in their experimental studies we assume that *the appearance of the characteristic changes in the QRS complex in precordial leads in anterior wall infarction involves two factors, namely: 1, the appearance of an initial negative deflection preceding the R wave, i. e., a Q wave, and 2, complete or partial abolition of the R wave.* While the first of these factors is present almost constantly in CF_2 as well as in IVF in the cases of anterior wall infarction observed by the writer, the second factor is very variable, giving rise to the many variations in the tracing of the *QRS* complex.

The explanation generally given of the *QRS* changes—that they are due to a complete absence or a marked diminution of the *R* wave—covers only some of the *QRS* complexes and is in most cases insufficient or even directly misleading. The explanation given here finds a quite essential support in the conditions observed in Lead I. For in typical cases of anterior wall infarction we find in this very lead the same two effects, appearance of a *Q* wave and diminution of the *R* wave.^{3,15,16}

Figure 2 gives a schematic presentation of the two ways in which a clear-cut central infarction curve may result from a normal diphasic *QRS* complex. The development outlined in *A* concerns merely a diminution of *R*, going on to complete absence of *R*. The development outlined in *B* implies the appearance of a *Q* wave together with diminution of *R*, going on to complete abolition of the latter. Although the final results of the two developments cannot be distinguished from each other, they are still brought about in two fundamentally different ways. It will be noticed that the different *QRS* complexes in Series *B* correspond closely to the *QRS* complexes obtained in clinical cases of anterior wall infarction (see Fig. 1), so that the mechanism of the process illustrated in *B* for the appearance of a classical infarction curve (Curve *B6*) is to be looked upon as the correct one.

It is a well-known fact that marked left preponderance and left bundle branch block (new nomenclature) may be associated with complete absence of *R* in CF_2 so that the *QRS* complex here cannot be distinguished from a classical infarction curve of central type (Fig. 1, *1d*). In a previous paper, the writer^{11b} has advanced the hypothesis that left inhibition of conduction gives rise to diminution of *R* in CF_2 , and that this phenomenon may go on to complete absence of *R*. It is this very mechanism that is outlined in Figure 2, *A*. The final result of this process (Curve *A6*) cannot be distinguished from the true infarction curve *B6* and yet it has to be characterized as a "false infarction curve."

From the preceding it is evident that a remnant of the *R* wave in marked left preponderance must present itself as a small initial *R* wave, whereas a remnant of the *R* wave in anterior wall infarction shows as a splitting of an initial negative deflection.

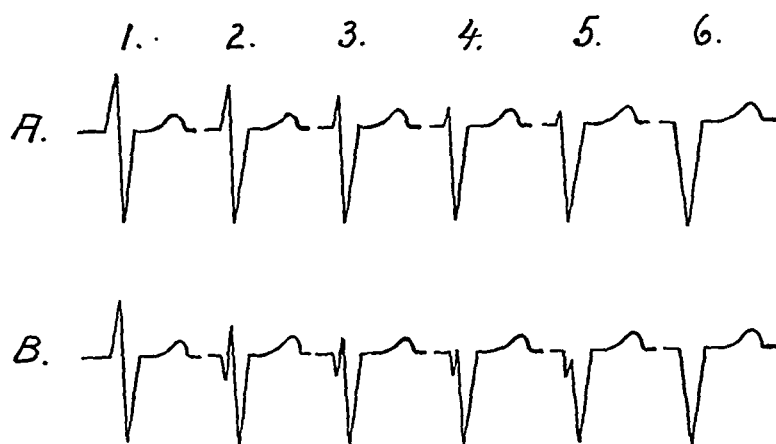


FIG. 2.—Schematic presentation of the two ways in which an infarction curve of classical "central" type conceivably may develop from a normal QRS complex in precordial leads. 1, Normal diphasic QRS complexes; A6, "false infarction curve" (which cannot be distinguished from B6); B6, classical infarction curve of "central" type; 2, 3, 4 and 5, transitional stages.

After this analysis of the QRS changes in anterior wall infarction there can be no particular relation between the abnormalities complete absence of the *R* wave and diminished initial *R* wave when we are dealing with cases of anterior wall infarction. Several investigations have been aimed at the occurrence of these abnormalities with a view to the diagnosis and differential diagnosis of anterior wall infarction.^{9,10,12} Presumably it would be more rational to investigate the significance of an initial negative deflection in precordial leads with or without a concurrent diminution of *R*.

It is not to be denied that a small initial *R* wave in precordial leads may be present in anterior wall infarction. In such cases we may imagine that one factor, the appearance of a *Q* wave, has failed while the diminution of *R* has asserted itself. It is to be emphasized, however, that such cases are rare as compared to the great number of cases which show an initial negative deflection, and that the former represent a considerable deviation from the characteristic changes. When we are dealing with anterior wall infarction the interest taken in a small initial *R* wave is generally greater than this abnormality deserves, at any rate when it is found in CF₂ alone. When this abnormality has been associated with the fundamentally different abnormality encountered in complete absence of the *R* wave (Fig. 2, B) observed in anterior wall infarction, no doubt it is largely because Bohning and Katz¹ have described a small initial *R* wave as characteristic of coronary sclerosis. It is to be emphasized, however, that in these studies they employed only a parasternal

lead, and that they state themselves that in nearly all the cases with a little *R* wave in this lead there was at the same time a left preponderance or intraventricular disturbance in the conductivity. As a small initial *R* wave in a parasternal lead is a frequent finding in left preponderance of various etiology (*e. g.*, aortic lesions too) it is not justified from Bohning and Katz's observations to attribute the presence of a small initial *R* wave to coronary sclerosis in particular.

Summary. 1. In most clinical works the typical *QRS* changes in precordial leads in anterior wall infarction are described in terms indicating absence or marked diminution of the *R* wave; in addition atypical split or W-shaped *QRS* complexes have been described. The occurrence of a normal *QRS* complex in IVF in anterior wall infarction has been reported too.

2. This paper gives a preliminary report on the changes in the *QRS* complexes in precordial leads in 23 clinical cases of anterior wall infarction observed by the writer. In these cases altogether 192 electrocardiograms were taken in the 3 conventional leads and in 2 precordial leads, CF_2 and IVF, from a few hours to several years after the acute injury. Twenty of the 23 cases showed an initial negative deflection in both CF_2 and IVF, and 2 other cases showed an initial negative deflection, either in CF_2 or IVF, in all the records. So this abnormality has to be looked upon as a very constant change in anterior wall infarction.

3. The *QRS* changes in precordial leads in anterior wall infarction are analyzed, and it is pointed out that these changes are far more characteristic than suggested by previous investigations. It must be considered erroneous to characterize the *QRS* changes in anterior wall infarction by absence of the *R* wave, as this explanation covers merely a minor part of the infarction curves (clear-cut central infarction curves), and it is insufficient to characterize the *QRS* changes in a good many cases, besides being directly misleading in some cases. On the other hand, practically all the *QRS* changes observed may be analyzed after common simple rules under the supposition that anterior wall infarction implies two factors: 1, appearance of a *Q* wave, and 2, diminution or complete disappearance of the *R* wave. The first of these factors is very constant, whereas the other is very variable, giving rise to the many variations in the features of the *QRS* complex.

4. The two ways in which a classical ("central") infarction curve may develop from a normal diphasic *QRS* complex are described (Fig. 2) and the conceptions "true infarction curve" and "false infarction curve" are introduced.

5. According to the writer's interpretation of the *QRS* changes in anterior wall infarction, a small *initial R* wave, which often is reckoned as equal to complete absence of the *R* wave in connection with anterior wall infarction, represents a considerable deviation from the typical changes. A small initial *R* wave in a parasternal

derivation is of no positive significance to the diagnosis of anterior wall infarction, as this abnormality is very common in marked preponderance of the left side of the heart.

6. The practical result of the view of the *QRS* changes in precordial leads in clinical cases of anterior wall infarction, as described here, will be that *particular attention must be paid to the presence of an initial negative deflection—with or without absence of the R wave—in the QRS complex in precordial leads.*

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ABSORPTION, EXCRETION AND DISTRIBUTION OF SULFADIAZINE (2-SULFANILAMIDO-PYRIMIDINE).*

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SULFADIAZINE (2-sulfanilamido-pyrimidine), the pyrimidine ana-
logue of sulfapyridine and sulfathiazole, is one of a group of hetero-
cyclic derivatives of sulfanilamide that have been synthesized by

* The chemical determinations were carried out by Betty Shaler Smith, Alice
Ballou and Edith Rathbun.

Roblin *et al.*⁵ The pharmacologic properties of this compound in laboratory animals and its therapeutic efficacy against experimental infections with a variety of bacteria were investigated by Finestone *et al.*² and were found to be of sufficient interest to warrant clinical study. *In vitro* experiments on the effect of this drug* on a variety of common pathogenic bacteria are under way in this laboratory, and its use in the treatment of various infectious diseases is now being evaluated in this clinic. Preliminary results suggest that sulfadiazine is probably considerably less toxic than any of the other common sulfonamides now in use and that it may have a wide range of efficacy. These results will be the subject of a separate communication. In this paper we present data concerning the absorption, excretion and distribution of this drug in human subjects.

Materials and Methods. The present studies were carried out in essentially the same manner as previous ones with other common sulfonamides.^{6,7} For the most part, male adults, convalescent patients who were afebrile and ambulatory and had normal renal function, were chosen as subjects. Some observations were also made on a number of patients under treatment with sulfadiazine. The subjects were maintained on a routine ward diet with a daily fluid intake of 3 to 4 liters. For the intravenous and subcutaneous injections, solutions of 5.0 and 0.5%, respectively, of sodium sulfadiazine in 0.85% sodium chloride were used. Ten minutes were taken for the former and $\frac{1}{2}$ to 1 hour for the latter injections. Oral doses were given with 500 ml. of water about 2 hours after breakfast. Rectal doses were suspended or dissolved in 400 or 500 ml. of warm tap water. A cleansing enema was given 4 or 5 hours before each rectal dose. No untoward reactions were noted in any of the subjects. Blood samples were taken at frequent intervals during the first 12 hours after each dose, and at 12- or 24-hour intervals thereafter. All urines were saved and collected at the same time as the bloods. Collections were continued until the urines showed only insignificant amounts of drug. Since blood levels were always below 1 mg. per 100 cc. after 48 hours and only small amounts were excreted in the urine after 72 hours, the data were charted only for these intervals. Quantitative determinations of the drug were made by the method of Bratton and Marshall,¹ using the Klett-Summerson colorimeter with a No. 540 filter. For assay of organs, tissues were weighed as soon as possible after removal and were later finely minced, ground with sand, and extracted 3 times with boiling distilled water which was then collected and treated as blood.

Blood Levels and Urinary Excretion After Single Doses. The findings are charted in Figures 1 and 2, and some of the more pertinent data are summarized in Table 1. A standard dose of 5 gm. was used to compare absorption and excretion from different routes, and a few observations were made on smaller oral doses. Maximum blood levels were attained immediately after the intravenous injections, 2 to 3 hours after the subcutaneous doses and 4 to 6 hours after the oral ones. Higher levels were reached in the blood and these were sustained longer than with either sulfanilamide, sulfapyridine or sulfathiazole.⁶ Moderate levels of sulfadiazine were

* Supplied by the Lederle Laboratories, Inc., and the American Cyanamid Company.

TABLE 1.—MAXIMUM BLOOD AND URINE CONCENTRATIONS AND URINARY EXCRETION OF SULFADIAZINE AFTER A SINGLE DOSE GIVEN BY VARIOUS ROUTES.

Route.	Subject.	Age (yrs.).	Weight (kg.).	Dose (gm.).	Maximum blood concentration.			Maximum urine concentration.				Urinary excretion.			
					Hours after adminis- tration.	Mg. per 100 cc.		Periods (hours after adminis- tration).	Volume (ml.).	Mg. per 100 cc.		% of administered drug recovered.		% of recovered drug conjugated.	
						Frec.	Total.			Frec.	Total.	24 hours.	72 hours.	First 24 hours.	24-72 hours.
Oral	F. R.	45	66	5	6	8.1	9.3	6-12	900	93.6	136.0	60.1	84.6	36.8	54.0
	B. B.	29	61	5	6	7.7	8.7	6-12	1060	51.6	69.1	32.6	61.7	26.4	49.3
	J. K.	60	61	5	4	7.9	8.6	12-24	400	143.0	273.6	59.7	77.8	39.5	26.6
	W. D.	35	56	5	4	10.8	12.1	6-12	1075	71.2	109.3	63.6	...	32.1	...
	T. B.	72	64	4	4	9.9	12.6	8-12	500	78.7	130.9	66.5	88.2	43.2	55.9
	B. R.	48	67	4	6	6.7	7.9	4-6	300	131.5	155.8	63.8	73.4	34.6	20.7
	P. M.	51	76	3	4	5.3	5.3	4-6	450	42.2	51.0	48.9	58.4	20.3	26.5
	J. D.	24	66	2	6	4.3	4.3	4-6	300	41.8	46.8	50.2	78.5	14.2	33.4
Intravenous*	O. R.	49	79	5	1†	13.1	14.2	2-4	300	61.6	80.5	55.0	68.0	24.8	30.3
	W. W.	49	55	5	1†	13.0	14.2	0-2	280	124.6	151.8	55.0	78.4	26.3	49.1
	A. R.	41	57	5	1†	19.9	20.9	4-6	150	372.9	435.2	73.0	85.9	19.4	33.0
Subcutaneous*	J. B.	44	65	5	3	11.0	11.9	4-6	100	288.0	318.5	72.0	92.2	6.8	33.1
	F. R.	45	66	5	2	9.2	9.2	6-12	600	88.8	119.7	67.0	83.7	26.2	48.2
Rectal	F. R.	45	62	5*	7	1.6	1.6	6-12	410	30.4	46.1	8.5	11.8	26.9	46.9
	R. J.	68	66	5	3	Trace	Trace	10-24	400	6.5	11.0	1.6	3.0	31.3	23.9

* Sodium salt given. The calculations are not corrected for sodium or water content.
† First observation.

still found after 12 hours, and appreciable levels were present at 24 hours, but only traces were detected in the blood at 48 hours. Absorption from the rectum, however, differed radically, and will be considered separately.

The maximum concentrations in the urine occurred soon after the maximum blood levels, and were therefore found earlier after the parenteral than after the oral doses. The proportion of administered drug recovered from the urine varied only slightly with the route of administration. About 60% of the administered drug was recovered from the urine in the first 24 hours and about 75% was recovered in 72 hours. (This amount is actually greater for the parenteral doses when allowance is made for the sodium and water content of the sodium salt.)

In a general way, the blood levels were also influenced by the body weight when the same dose and route was used. With different sized oral doses, the maximum blood concentrations were roughly proportional to the dose. There were wide individual variations in absorption and distribution, however, as indicated by the differences in the maximum levels and in the time when they were attained.

Rectal Administration. Very little of the drug was absorbed after rectal administration in 5 subjects. The data of 2 of these are shown in Table 1. When 5 gm. of powdered sulfadiazine were given in suspension, only traces were detected in the blood. Less than 4% of the administered drug was recovered from the urine and about 50% of the drug was recovered unaltered in the first stool passed 36 hours after administration. When 5 gm. of sodium sulfadiazine was given rectally as a 1% solution in physiologic sodium chloride, maximum blood levels of 1.6 to 2.8 mg. per 100 cc. were reached, but less than 15% was recovered from the urine.

Acetylation (see Table 1 and Figs. 1 and 2). Only small proportions of the total concentration of the drug were found in the blood in conjugated form and, in most subjects, from 20 to 35% of the total amount of the drug administered was recovered from the urine in this form. In general, the lower figures were obtained after parenteral doses. There were, of course, considerable individual variations. Unlike the other common sulfonamides, the proportion of the conjugated drug did not tend to show a steady increase. In fact, in a number of subjects the conjugated form of the drug was apparently excreted more rapidly than the free form. This was evidenced by the decline in the proportion of conjugated drug in the blood and in the urine, after the first 24 hours.

Distribution of Sulfadiazine Between Plasma and Red Blood Cells (Table 2). Oxalated blood was used and was taken from a number of subjects following an intravenous injection of sodium sulfadiazine. This method was chosen because previous experience with other sulfonamides has indicated that *in vitro* addition of drugs to blood may be unsatisfactory due to the uncertainty of effecting complete

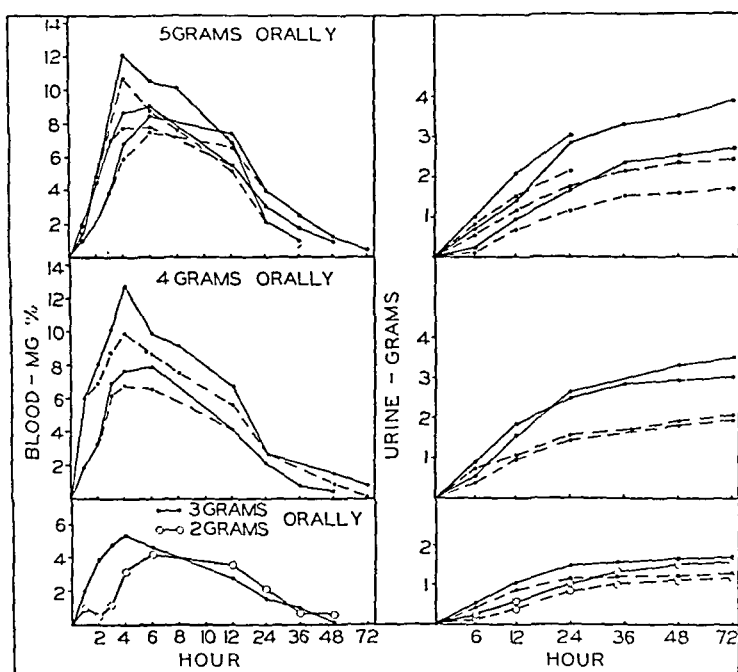


FIG. 1.—Blood levels and cumulative urinary excretion of sulfadiazine after single oral doses. Dotted lines = free; solid lines = total (free + conjugated).

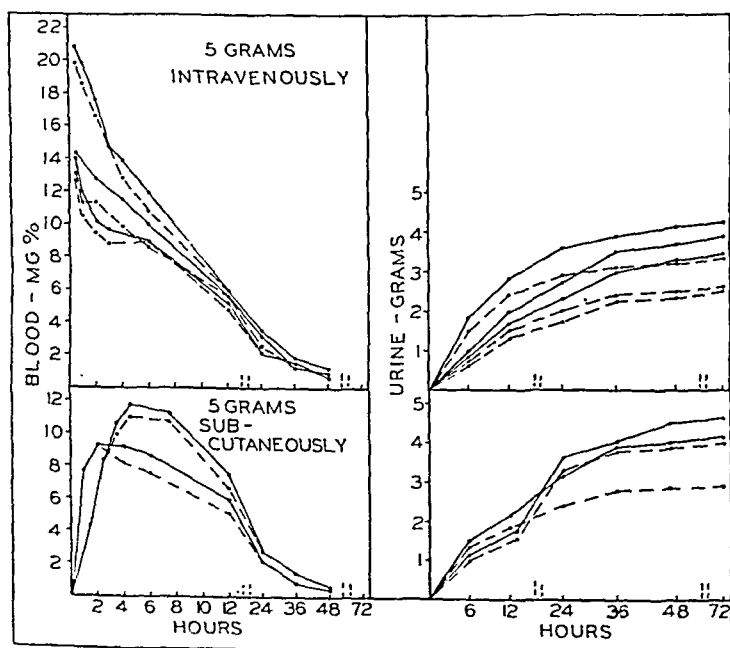


FIG. 2.—Blood levels and cumulative urinary excretion of sulfadiazine after a single parenteral dose of sodium sulfadiazine. Dotted lines = free; solid lines = total (free + conjugated).

solution. The present data indicate that sulfadiazine is found in greater concentration in plasma than in the red blood cells. It is thus distributed in the same manner as sulfathiazole, and unlike the more uniform distribution of sulfanilamide and sulfapyridine.⁶ The equilibrium is reached rapidly, as in the case of the other common sulfonamides.^{6,7} Estimations based on data similar to those already presented indicate that sulfadiazine, like sulfathiazole, is distributed in the body in a volume greater than the extracellular fluid but considerably less than the total body water.

TABLE 2.—DISTRIBUTION OF SULFADIAZINE BETWEEN PLASMA AND RED BLOOD CELLS.

Subject.	Hours after dose.*	Sulfadiazine concentration.				P/C.	Hematocrit.
		Free or total.	Whole blood.	Plasma (P).	Cells (C) calculated.		
B. B.	4	Free	6.0	8.9	3.5	2.5	54.1
		Total	6.7	9.8	5.1	2.4	
T. B.	4	Free	9.9	12.1	6.4	1.9	39.2
		Total	12.6	14.3	10.0	1.4	
B. R.	4	Free	6.9	9.0	4.0	2.3	39.0
		Total	9.7	10.1	3.6	3.0	
T. D.	3	Free	12.3	14.1	9.4	1.5	35.6
		Total	14.0	17.0	9.2	1.8	
	6	Free	9.9	12.9	5.0	2.6	
		Total	12.2	15.2	7.0	2.2	
J. H.	4	Free	7.2	8.7	5.1	1.7	41.3
		Total	8.0	9.8	5.6	1.8	

* A single dose of sodium sulfadiazine was given intravenously to each subject except to J. H., who was receiving sulfadiazine, 1 gm. every 4 hours, and the blood was taken 4 hours after one of the doses on the 3d day.

Distribution of Sulfadiazine in Body Fluids and in the Tissues. Simultaneous levels of blood and other body fluids taken from different subjects at various intervals following single intravenous injection.

TABLE 3.—COMPARISON OF SIMULTANEOUS CONCENTRATIONS OF SULFADIAZINE IN BLOOD AND IN BODY FLUIDS AFTER A SINGLE INTRAVENOUS INJECTION OF 5 GM. OF SODIUM SULFADIAZINE.

Patient.	Weight (kg.).	Hours after injection.	Fluid.	Sulfadiazine concentration.				
				Blood.		Fluid.		% of blood level (free).
				Free.	Total.	Free.	Total.	
S. K.	79	1	Spinal	9.1	10.0	1.9	1.9	21
M. C.	60	3	Spinal	14.6	16.0	3.1	3.1	21
R. L.	77	5	Spinal	9.2	10.8	3.8	3.8	41
M. M.	70	8	Spinal	5.2	6.2	3.4	3.4	65
J. M.	60	7	Pleural	6.1	6.9	3.8	3.8	62
E. P.	69	6	Ascitic	5.8	6.4	4.9	4.9	86

tions of the sodium salt are given in Table 3. There was a steady increase in the concentration of sulfadiazine in the spinal fluid relative to the corresponding blood levels. This is, of course, difficult

to interpret accurately because of the steady decline of the blood levels following the intravenous injections, as shown in Figure 2. However, during the course of therapy with regular 4 hourly doses, simultaneous determinations indicate consistently high concentrations in the spinal fluid, averaging two-thirds or more of the corresponding blood levels, as shown in Table 4. In this respect, sulfadiazine is similar to sulfapyridine and sulfanilamide and differs from sulfathiazole. With the latter, spinal fluid concentrations are usually about one-third of the corresponding blood levels.⁶ In single determinations of pleural and synovial exudates the concentrations were higher than the levels in the blood drawn at the same time, although great care was taken to avoid contamination of the exudates with novocaine.

TABLE 4.—COMPARISON OF SIMULTANEOUS LEVELS OF SULFADIAZINE IN BLOOD AND SPINAL FLUID IN PATIENTS RECEIVING THERAPEUTIC DOSES.

Patient.	Diagnosis.	Day of treatment.	Sulfadiazine concentration.				% of blood-level (free).
			Blood.		Spinal fluid.		
			Free.	Total.	Free.	Total.	
P. S.	Pneumococcic meningitis	2	6.4	7.1	5.4	6.2	84
		4	6.5	6.5	5.4	6.0	83
		5	5.4	6.0	5.1	5.1	94
		8	1.5	2.7	1.1	1.1	73
C. B.	Meningococcic meningitis	1	2.7	4.3	1.7	3.1	67
		2	10.3	11.7	6.7	7.3	66
		5	13.2	18.6	10.4	11.8	78
T. L.	Cerebral thrombosis	2	4.9	4.9	2.3	2.3	49
		3	9.0	10.7	6.2	6.2	68
		6	7.2	7.9	5.0	5.0	69
		8	6.4	7.0	4.0	4.0	62
D. M.	Pleurisy with effusion	2	7.8	8.4	9.3*	10.3*	119
R. N.	G.C. arthritis	6	7.7	9.7	14.6†	16.4†	189
	* Pleural fluid.				† Synovial fluid.		

† Synovial fluid.

There was an opportunity to study the concentration of sulfadiazine in various organs and body fluids of 5 patients who died during therapy. The autopsy in Case I was limited to the head. The levels indicated that, for the most part, the drug was distributed throughout the body. The urines, of course, showed concentration of the drug, both free and conjugated. Spinal fluids contained about two-thirds the blood concentration, while the levels in pleural and pericardial fluids approximated the blood more closely. The concentrations in brain were from one-third to one-half the amounts found in blood. The kidney in Case II contained more than twice the blood levels, thus simulating the findings in sulfapyridine and sulfathiazole treated cases. In 3 other cases the concentration of drug in kidney tissue was about the same as that of blood and liver, thus resembling the findings in cases treated with sulfanilamide.⁶ Some of the variations noted may be due to errors involved in the method.

Blood and Urine Concentrations During Sulfadiazine Therapy. Blood concentrations were usually sustained at higher levels than with any of the other common sulfonamides given in similar doses. This is evident when Figure 3 is compared with previous similar charts for sulfapyridine⁴ and sulfathiazole³ treated patients. In fact, the levels maintained on sulfadiazine doses of 1 gm. every 6 hours were generally higher than those obtained with 1 gm. every 4 hours of

TABLE 5.—DISTRIBUTION OF SULFADIAZINE IN ORGANS AND BODY FLUIDS OF 5 PATIENTS WHO DIED WHILE UNDER TREATMENT WITH THIS DRUG.

Organ or fluid.*	Sulfadiazine concentration (mg. per 100 cc.).									
	Case I.		Case II.		Case III.		Case IV.		Case V.	
	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.
Blood	1.5	2.7	8.0	10.1	20.8	24.6	7.2	8.3
Spinal fluid . . .	1.1	1.1	7.8	8.1	11.6	15.2	14.7	15.4	3.8	4.4
Pleural fluid . . .	1.5	2.1	19.4	23.9
Pericardial fluid	20.0	23.2
Urine	88.9	103.2	85.8	121.9
Brain	0.8	0.8	2.6	2.6	7.0	7.9	8.7	9.7	2.4	2.4
Spleen	5.6	5.6	9.4	15.8	14.2	17.1	5.6	5.6
Liver	7.1	8.6	12.8	18.7	12.6	14.8	5.7	7.3
Lung†	8.7	10.0	10.0	15.0	15.8	19.0	7.9	8.7
Kidney	19.9	26.4	13.0	21.1	16.4	19.7	7.0	9.2

* Determinations in bile were unsatisfactory, and are not recorded.

† Consolidated lung chosen when available.

Case I: P. S., male of 67, pneumococcus Type XIX meningitis, died after receiving 50 gm. of sulfadiazine in 8 days. Treatment was irregular during the last 2 days.

Case II: J. D. male of 28, pneumococcic Type VII pneumonia, received 5 gm. orally after initial intravenous injection of 5 gm. of sodium salt and died 18 hours after first dose.

Case III: L. R., female of 55, pneumococcus Type VII endocarditis, received 42 gm. in 6 days. Underlying aortic stenosis (rheumatic).

Case IV: J. R., female of 57, atypical pneumonia (lung culture: *Staph. aureus*). Received 5 gm. sodium salt intravenously and 35 gm. orally.

Case V: J. S., male of 47, meningococcus meningitis, received 8 gm. orally and died 16 hours after admission.

the other common sulfonamides. For the most part the levels were more than twice as high as those found in sulfathiazole treated cases. A more or less uniform concentration of sulfadiazine was maintained after the first day by most of the subjects, while fluctuations occurred in others. The percentage of conjugation of the drug in the blood was usually low and did not tend to increase and, in some patients, even decreased as therapy was continued, as was anticipated from the findings in Figures 1 and 2. The high levels were not associated with nitrogen retention or with other evidences of renal impairment. Vomiting did not occur in any of the patients whose levels are shown in the figure and they all took fluids liberally, so that these factors likewise did not contribute to the high levels.

Concentrations of sulfadiazine were determined in urine samples collected at random from a number of patients who were receiving doses of 1 gm. every 4 or 6 hours. In specimens obtained after the second day of treatment, the drug levels ranged from about 100 to about 500 mg. per 100 cc., of which from 10 to 63% was conjugated. There was no correlation between the total concentration and the per cent of conjugation. In fact, some of the urines with the lowest concentrations of drug showed the highest per cent of conjugation. While crystals of drug (probably acetylsulfadiazine) were observed both in urines containing high levels and in those with low concentrations, hematuria, gross or microscopic, and nitrogen retention attributable to the drug have not been noted thus far.

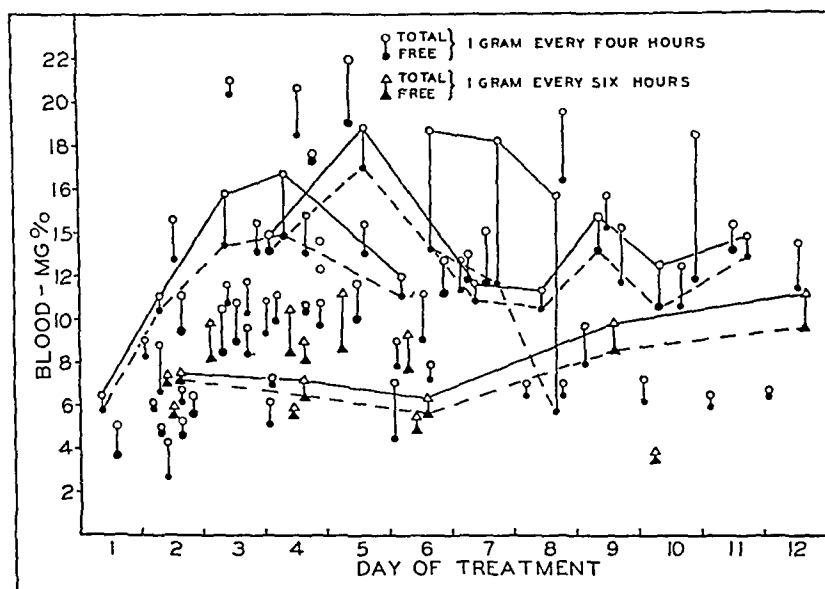


FIG. 3.—Concentrations of sulfadiazine in the blood of patients at various intervals after the beginning of treatment. For some of the patients, determinations made at different intervals are connected.

Renal Clearance. Calculations of the clearance values for sulfadiazine after intravenous injections showed considerable variations in different subjects. In each instance, however, the results indicated that there was considerable tubular reabsorption of the drug.

Comment. A number of interesting features concerning the absorption and excretion of sulfadiazine have been brought out in the data presented. 1. Higher concentrations of sulfadiazine are reached and are maintained longer in the blood from single and from repeated doses, when compared with the levels obtained with the other common sulfonamides given in similar doses. This suggests that doses of this drug may be given at greater intervals than is usually required with other drugs. 2. Acetylation of sulfadiazine does not tend to increase during the course of treatment, even when

high levels are maintained. 3. The drug appears in high concentrations in spinal, pleural and ascitic fluids.

In our experience to date, more than 100 patients have received this drug, without any evidence of severe toxic effects. The gastrointestinal symptoms and the mental depression which are characteristic of sulfapyridine therapy, and which are also frequently noted with sulfanilamide and sulfathiazole, have been notably absent in patients treated with sulfadiazine. In severely ill patients receiving the latter drug, marked subjective improvement has usually preceded the fall in temperature and pulse rate, while the reverse is more frequently the case with the other sulfonamides. A nodular erythema similar to, but less marked than those frequently seen in sulfathiazole treated patients, was noted in one patient. These findings alone justify continued clinical trials with this drug.

Obviously, it will be necessary to study carefully a considerably larger number of cases before reliable comparisons with other sulfonamides will be justified. It will suffice to say that this drug appears to be as efficacious as sulfapyridine and sulfathiazole in most of the conditions in which it has been used. Of the patients treated in this clinic, about one-half were cases of lobar pneumonia.

Since this paper was written there have appeared two papers concerning absorption and excretion of sulfadiazine. Plummer and Ensworth* studied blood levels and urine excretion in 4 subjects following the oral administration of a single 2-gm. dose. Reinhold *et al.*† have presented data concerning the fate of a single 3-gm. dose given orally in 10 subjects. The former authors made observations in 8 patients and the latter in 20 patients receiving therapeutic doses. The data presented by these workers are similar to the corresponding data presented in this paper.

Summary. Data are presented concerning the absorption and excretion of sulfadiazine after single and repeated doses. Higher blood levels are reached and these are more sustained than with any of the other common sulfonamides (sulfanilamide, sulfapyridine and sulfathiazole). Conjugation of sulfadiazine in the blood is usually slight and there is no tendency for the conjugated drug to be retained. The distribution of sulfadiazine in various tissues and between red blood cells and plasma is similar to that of sulfathiazole. In its penetration into the spinal fluid, sulfadiazine resembles sulfanilamide and sulfapyridine. Sulfadiazine is not absorbed to any appreciable extent after rectal administration, and the sodium salt is only slightly absorbed from that route.

Preliminary clinical experience indicates that nausea, vomiting and mental depression are notably absent in patients treated with

* Plummer, N., and Ensworth, H. K.: *Proc. Soc. Exp. Biol. and Med.*, **45**, 734, 1940.

† Reinhold, J. G., Flippin, H. F., Schwartz, L., and Domm, A. H.: *AM. J. MED. SCI.*, **201**, 106, 1941.

sulfadiazine, and other serious toxic effects have not been encountered thus far. The therapeutic results in patients with pneumonia and a variety of other infectious diseases suggest that the drug has considerable efficacy. These findings indicate that further clinical trials with this drug are justified.

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A COMPARISON OF THE MORTALITY IN PNEUMOCOCCIC PNEUMONIA TREATED BY HYDROXYETHYLAPOCUPREINE AND BY SULFAPYRIDINE.

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In this article we wish to compare the mortality of pneumonia from our hospital for the year 1939-40, as treated by hydroxyethylapocupreine and by sulfapyridine, and to summarize our results in the treatment of pneumonia by hydroxyethylapocupreine over a 5-year period, 1935-40.

In our last clinical report³ we stated that we had observed no evidence of any serious toxic action in the use of hydroxyethylapocupreine on patients with pneumonia. The past 2 years' experience further confirms this fact. The patients studied, to a very large extent, were, as previously, individuals from the public wards of the Mercy Hospital, Pittsburgh. There are no postoperative cases nor any children under 15 years of age included in our tables. Patients dying within 24 hours of admission, both in the treated and no specific treatment groups, were eliminated. We believe little information in therapy is to be obtained from moribund cases.

During the past 2 years, 1938-40, we have seen many examples in our pneumococcic pneumonia cases of mixed infection with the *Strep. hemolyticus*, *Staph. aureus* and *H. influenzae*. In the past year and a half, particularly, the increase in the incidence of *Staph. aureus* has been noteworthy. The bacteriology of our cases will be reported by one of us (M. M. B.) in a separate paper. We have no observations on virus studies of the sputum but from the clinical point of view the common cold in all grades of severity has been very prevalent during the past year. We have seen many examples of a rather severe acute respiratory infection since December, 1936, which we have called influenza, possibly for want of a better term. This infection during the past winter in its early stages was very difficult to distinguish from an early pneumonia, as an initial chill was frequent at the onset. Furthermore, repeated chills in the first 24 to 48 hours were commonly observed in this infection. Roentgen ray studies showed heavier than normal lung markings but no consolidation. Breath sounds might be depressed but the lungs were often dry, or had very few râles. The temperature usually fell to normal spontaneously in 2 to 5 days but some cases showed fever for a week or 10 days with no physical or Roentgen ray signs of consolidation. A few patients with this infection were treated with hydroxyethylapocupreine or with sulfapyridine, and reactions similar to those observed in the spontaneously recovered group were noted, either a dramatic fall in fever or no shortening whatsoever of the febrile period. We have, therefore, eliminated all of these cases from our pneumonias. On account of the severe chill at the onset they could be easily confused with a true pneumonia. Roentgen rays have been invaluable in diagnosis of this group of cases. As these cases have no mortality, unless a secondary pneumonia develops, one should be extremely careful in separating them from true pneumonic infections. On the other hand, we believe we have had in a few instances during the past 2 years very prompt recoveries in cases when hydroxyethylapocupreine was given immediately or within a few hours after the initial chill. We have previously referred³ to this type of case. However, unless Roentgen ray evidence was positive for pneumonic consolidation they have not been included in our tables.

TABLE 1.—ANALYSIS OF PNEUMONIA CASES, 1938-1939.

	No. of cases.	Deaths.	Mortality percentage.
No specific treatment	34	16	47
Hydroxyethylapocupreine . . .	86	18	21
<i>Bacteremic Cases.</i>			
No specific treatment	15	11	73
Hydroxyethylapocupreine . . .	20	10	50
<i>Non-bacteremic Cases.</i>			
No specific treatment	19	5	26
Hydroxyethylapocupreine . . .	49	6	12

This table is given merely to complete the published sequence of yearly mortality figures since 1935-36. There were 17 hydroxyethylapocupreine cases in this year treated outside of our hospital that did not have blood cultures taken, hence the difference in the sum of figures for the bacteremic and non-bacteremic cases, as compared with the total figures, is accounted for. The no-blood culture group was larger in this year than in any other.

TABLE 2.—ANALYSIS OF PNEUMONIA CASES, 1939-1940.

Group.	Per cent positive blood cultures.	Total.			Positive blood cultures.			Negative blood cultures.		
		Cases.	Death.	Per cent.	Cases.	Death.	Per cent.	Cases.	Death.	Per cent.
1. Hydroxyethylapocupreine	25	51	7	14	13	4	31	38	3	8
2. Hydroxyethylapocupreine and sulphone glucose derivative	43	28	12	43	12	6	50	16	6	37
3. Combined 1 and 2	32	79	19	24	25	10	40	54	9	17
4. Sulfapyridine	16	31	7	22	5	2	40	26	5	19
5. No specific treatment	33	13	39	2	2	100			

In 7 cases without specific treatment blood cultures were not taken and all of this group were fatal. It is probable that some or many of these cases would have had positive cultures, hence we have omitted the percentage of positive blood cultures in the table in Group 5, as the very low incidence of 2 positive blood culture cases in 26 (8%), gives probably a false reading. Similarly the mortality percentage figure for the negative blood culture cases, 24 cases with 4 deaths (17%) is also inaccurate. The mortality percentage, however, in the positive blood culture cases of Group 5 would not be changed.

Table 2 shows the mortality figures for the past year 1939-40. A comparison of the mortality of cases treated by hydroxyethylapocupreine or sulfapyridine is the main point which we wish to emphasize. In this year both groups are taken almost entirely from our hospital. The table requires some detailed explanation. In Group 1 hydroxyethylapocupreine was used alone. The mean age for this group was 39 years which probably in part accounts for the lower mortality. However, the bactremia incidence was considerably higher than in the sulfapyridine group, and the mortality in the bacteremic cases was lower. Group 2 in addition to hydroxyethylapocupreine received, simultaneously, a sulphone glucose derivative. These 28 cases were treated in the first half of the year since after that time this procedure of therapy was discontinued for reasons mentioned later. We had decided that all patients with pneumonia over 60 years of age and all cases showing positive blood cultures were to have not only the hydroxyethylapocupreine by

mouth, but also the sulphone glucose derivative intravenously. The mean age for Group 2 was 61 years, and 43% showed positive blood cultures, obviously indicating a very serious problem for therapy. We were convinced after trial, experimental and clinical, that the sulphone glucose derivative was ineffective in the dosage given and that all favorable therapeutic action could be attributed to the hydroxyethylapocupreine. It is not considered necessary to go into the experimental details in this paper but one can state that this sulphone glucose compound is very effective by mouth in protection of mice against the pneumococcus injected intraperitoneally, but has very little protective action when the chemical is given subcutaneously. Further, the chemical by the subcutaneous route is very much less toxic for mice than by mouth. Intravenously the sulphone glucose was non-toxic even in very large doses to man or experimental animals. We gave from 1 to 2 gm. every 3 hours in pneumonia cases over a period of 3 to 5 days. There was not only no suggestion of toxicity, but also no favorable therapeutic action which one could clearly observe that would not be expected to occur with hydroxyethylapocupreine alone. For this reason it was discontinued in our pneumococcic pneumonias. Finland² has reported findings indicating that sulfapyridine glucose when given by mouth is active against the pneumococcus, and shows the usual toxicity but when it is given by vein both the potency and toxicity are lost. He stated that sulfapyridine glucose was inert by the intravenous route. In Group 3 we have combined the results of hydroxyethylapocupreine alone with the hydroxyethylapocupreine and sulphone glucose, as we believe this gives a more accurate figure for the whole hydroxyethylapocupreine group, and is certainly comparable to the sulfapyridine series. We would direct attention to the fact that there is almost double the incidence of bacteremia in the hydroxyethylapocupreine series (Group 3) as in the sulfapyridine group. The mean age for the combined hydroxyethylapocupreine cases was 46, while that for sulfapyridine was 56. Treatment began in the hydroxyethylapocupreine group in the 2.15 day (average) of the disease while in the sulfapyridine it was on the 2.9 day. The duration of fever in the recovered cases as estimated by the mean figure in the hydroxyethylapocupreine group was 9 days, in the sulfapyridine 7.5 days, while in the no specific treatment cases it was 13.5 days. The fever data is taken entirely from rectal temperatures. The prolongation of fever in recovered pneumonia cases during the past 3 years has been noted frequently. We believe this finding is associated bacteriologically with the presence of mixed infection and pathologically with the process of delayed resolution, and interstitial pneumonitis so characteristic of mixed infections in the lung.

Seventy-two per cent of the positive blood cultures had occurred by the third day of the disease in the hydroxyethylapocupreine

treated cases (Group 3) and 64% were present before the treatment began. Forty per cent of the sulfapyridine cases showed positive blood cultures by the first 3 days of the infection while 80% of their number were present before treatment had begun. There were 5 times as many bacteremia cases in the hydroxyethylapocupreine series as in the sulfapyridine group, although the total number of cases (bacteremic and non-bacteremic) in the former was only two and a half times more than in the latter.

In the recovered positive-blood-culture cases treated by hydroxyethylapocupreine over a period of 5 years, 1935-40, there were 11 in 142 cases with colony counts over 15. In the past year there were 4 in 25 cases, in 2 of these cases high counts of 130 and 359 respectively were recorded. The sulfapyridine series of 5 bacteremic cases showed 1 count of the 26 colonies in the recovered group.

In 12 postoperative pneumonia cases treated by sulfapyridine there were 4 deaths (33% mortality). These postoperative cases are not included in our tables. This is mentioned merely to indicate that in no group of pneumonic cases treated by sulfapyridine in our hospital have we seen the excessively low mortality figures (below 10%) described in the literature.

TABLE 3.—ANALYSIS OF PNEUMONIA CASES, 1935-1940.

	No. of cases.	Deaths.	Mortality percentage.
No specific treatment . . .	203	97	48
Hydroxyethylapocupreine . .	494	119	24
<i>Bacteremic Cases.</i>			
No specific treatment . . .	58	47	81
Hydroxyethylapocupreine . .	142	81	57
<i>Non-bacteremic Cases.</i>			
No specific treatment . . .	133	38	28
Hydroxyethylapocupreine . .	296	33	11

Table 3 requires little explanation. Again we call attention to the fact that the difference in the sum of the figures of the bacteremic and non-bacteremic cases and the total number, is accounted for by those cases during the past 5 years that did not have blood cultures taken. Of the 142 bacteremic cases, treated by hydroxyethylapocupreine, 42% were Type II, 11% Type I and 9% Type III pneumonias.

TABLE 4.—MORTALITY ACCORDING TO DAY OF DISEASE WHEN FIRST TREATED, 1935-1940.

	No. of cases.	Deaths.	Mortality percentage.
First day	103	25	24
Second day	79	28	35
Third day	190	34	18
Fourth day	73	21	29
Fifth plus day	38	11	29

This table, for the 5-year period, indicates as previously noted, that cases treated on the 3d day of the disease showed a somewhat

lower mortality. There were 11 cases where the day of the disease could not accurately be estimated.

TABLE 5.—SERUM AND COMBINED CHEMICAL TREATMENT CASES, 1939-1940.

	Cases.	Deaths.	Blood cultures.			
			Pos.	Deaths.	Neg.	Deaths.
Serum	1	0	1	0		
Serum and hydroxy.	4	1	1	1	3	0
Serum, sulfapyridine	6	2	2	2	4	0
Serum, hydroxy., sulfapyridine	1	1	1	1		
Hydroxy., sulfapyridine	9	2	3	2	6	0

Not included in any of the previous tables there were, during the past year, 11 cases that received serum and chemical therapy, in addition to 1 case which had serum alone, and 9 cases which received both hydroxyethylapocupreine and sulfapyridine. The amount of serum was in all cases in excess of what is generally considered as an adequate dose and was given comparatively early in the infection while the chemicals were used simultaneously with the serum, except in 1 instance when both sulfapyridine and hydroxyethylapocupreine were used in succession. As a group these serum and chemical treated cases were severe infections as the table indicates. The chemicals were given in a full dosage at least over a 24-hour period, but they were never given at the same time. In most instances hydroxyethylapocupreine followed sulfapyridine when the latter produced so much nausea and vomiting as to make further administration impossible. It has been our belief that a certain number of severe pneumonic infections can be saved only by a combination of serum and chemotherapy. It will be noted in this group of 21 patients that of the 12 cases treated with serum, 4 died (33%); of the 14 receiving hydroxyethylapocupreine 4 died (28%), and of the 16 who were given sulfapyridine, there were 5 deaths (31%). As the mortality figures for each chemical are about equal in Table 5, the exclusion of these cases would not alter the comparative mortality figures of Table 2 to any great extent.

The comparison of hydroxyethylapocupreine and sulfapyridine in the treatment of pneumonia cases during the past year in our hospital has been of interest. Certainly the figures given in Table 2 indicate that the two chemicals were practically equal in their therapeutic action. Further, there is some evidence to show that one group (hydroxyethylapocupreine) was composed of more severe infections as noted in the bacteremia incidence. The sulfapyridine group, on the other hand, were on the average a little older which would be less favorable to this chemical. We have been informed that our mortality rates in hydroxyethylapocupreine-treated cases have been considered excessively high, despite our published data³ to indicate that the chemical figures were practically equal to the serum-treated cases in Pittsburgh as published by the Department of Health of the City of Pittsburgh. It may be of interest to note

that the recent report of the City of Pittsburgh's Health Department for the past 3 years gives a 19% pneumonia mortality for serum-treated cases. The serum of generally accepted high potency is supplied free but is not given if the pneumonic infection is beyond the 3d day. In other words, the great majority of the serum cases, from which the records are compiled, are not late or moribund cases. The literature indicates many similar comparisons during the past 2 years of serum and sulfapyridine with the resulting figures about equal, providing the serum was given before the end of the 4th day. We were, therefore, very interested in comparing the results of treatment by the two chemicals hydroxyethylapocupreine and sulfapyridine during the past year in cases under our observation. Table 2 gives data which we are unable to interpret as showing sulfapyridine to be superior to hydroxyethylapocupreine. This is in agreement with our recently published experimental data¹ comparing the two chemicals in mouse protection studies. Also we have entirely failed to attain low mortality figures, 10% or under, with sulfapyridine. From our point of view such desirable figures can only be observed in communities having an excessively mild pneumonic infection, and relatively small percentage of poor human material in the total number of cases studied. We assume also that great care is taken to eliminate from pneumonia data influenza-like infections which may be extremely difficult to differentiate from pneumonia and which possess little or no mortality. We refer only to the adult patient.

During the past 2 years, in our material at least, there has been a high incidence of *Strep. hemolyticus* infection associated with the pneumococcus. This should produce a picture more favorable to sulfapyridine, as the hydroxyethylapocupreine has very little if any action on the *Strep. hemolyticus*. We have used the base of the hydroxyethylapocupreine during the past 2 years in the same dosage as previously stated, 15 grains every 3 hours. We do not believe any case needs more than 4 days' treatment, at least, if they are going to be influenced favorably it will be shown by that time. There is very little nausea or vomiting, in marked contrast to sulfapyridine. We saw a number of instances in which nausea and vomiting prohibited the further use of sulfapyridine even after attempting to repeat the dosage, while 3 cases of gross hematuria were noted. The absence of any serious toxic action of hydroxyethylapocupreine is of clinical importance. There has been no evidence of visual disturbance.

Conclusions. 1. In a series of cases of pneumonia treated during the past year, 1939-40, we found practically an equal mortality in cases treated by hydroxyethylapocupreine and by sulfapyridine.

2. A summary of the results of treatment of 494 pneumonia cases by hydroxyethylapocupreine for the past 5 years, 1935-40, is given. A marked lowering of the total mortality, and of the mortality in both the bacteremic and non-bacteremic cases has been shown.

3. The only evidence of toxicity observed in the 494 patients treated with hydroxyethylapocupreine has been occasional nausea and vomiting which was considerably less with the use of the base than with the dihydrochloride of this compound. There has been no evidence of visual disturbance.

The authors wish to express their thanks to Dr. H. H. Permar for his help during the past year.

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THE USE OF SYNTROPAN IN PARKINSONISM.*

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ENCEPHALITIC parkinsonism is a neurologic disorder which during the last two decades has become a major therapeutic problem. There is at present throughout the world an increasing number of unfortunate victims suffering from progressive incapacity due to chronic encephalitis. It is not necessary in this paper to discuss the pathogenesis and pathology of encephalitic parkinsonism. Justifiably in recent years a great deal of attention has been directed by neurologists to the problem of discovering new remedies which might arrest the progress or alleviate the symptoms of this dread condition.

The various forms of therapy which have been used may be divided into two groups. First, there has been therapy designed to halt the spread of neural involvement by destruction of the etiologic agent. As examples of this type of treatment may be mentioned various fever-producing agents, vaccines, Roentgen therapy, and so on. Commendable as they have been, one must regretfully admit that all of these attempts have failed this far.

The second group may be referred to as consisting of the symptomatic forms of therapy. They are designed to alleviate the unpleasant manifestations of the disease. In contrast with the negative results noted in the first group it is possible to state that definite

* The Syntropan used in this study was supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

success has been obtained by the use of a variety of symptomatic remedies. Among these may be mentioned such drugs as stramonium, hyoscine, atropine and benzedrine.

Recently it has been generally conceded that atropine and the closely related belladonna preparations constitute the most effective forms of symptomatic treatment available at the present time. The beneficial result is quite remarkable in some instances enabling totally incapacitated patients to resume a considerable degree of activity. Unfortunately, however, the toxic manifestations of atropine are apt to occur so often and to be so unpleasant that in many instances the use of the drug has had to be discontinued. In view of this undesirable situation, when a synthetic and apparently less toxic atropine preparation became available this study was conceived in order to determine the therapeutic effectiveness of such a preparation. The drug used has been the tropic acid ester of 2, 2-dimethyl-3 diethylamino-propanol (syntropan).

Procedure. A group of 16 patients having parkinsonism were treated with syntropan for periods varying from 10 days to 8 months. Five patients were observed in the wards and 7 patients in the out-patient department of this hospital; 4 were patients from private practice. In all instances during the period of observation, therapy was restricted to the drug under investigation, namely syntropan. In most instances it was possible to compare the effectiveness of this drug with antecedent or subsequent therapy.

While receiving syntropan all patients were seen at regular intervals, usually once a week. An objective evaluation of the neurologic status was made by examination of pupils, speech, posture, gait, muscle tone and tremors. Subjective alterations in the patients' conditions were evaluated by inquiry regarding the following features: salivation, oculogyric crises, degree of activity, and general state of health.

In addition, special attention was directed toward the determination of the character and intensity of toxic manifestations. This was done by means of questions as to the occurrence of: blurred vision, flushed face, dryness of pharynx, palpitation, nausea and vomiting, bowel dysfunction, dysuria, vertigo, lethargy, amnesia and confusion, hallucinations. The pulse rate and weight were recorded at each interview. In several cases frequent electrocardiographic examinations were made.

Results of Treatment. The drug used in this investigation (syntropan) has previously been considered chiefly from the standpoint of its effectiveness as an antispasmodic remedy. In this respect it has been reported by a number of authors as possessing the same qualities as atropine, while in therapeutic doses it is not apt to produce the undesirable by-effects which so commonly follow effective doses of atropine. In a comparative pharmacologic study Fromherz² discovered that the spasmolytic action of syntropan on smooth muscular organs, especially on the intestine, was about 20 times less than that of atropine. On the other hand, the action of syntropan on the pupil, salivary secretion and vagus was more than 100 to 1000 times less than that of atropine. Therefore, Fromherz concluded that syntropan was clinically useful as an antispasmodic remedy.

The literature discloses a few scattered reports of cases in which syntropan has apparently been found to be beneficial in the treatment of parkinsonism. Chiabov¹ partially replaced atropine by syntropan in 3 cases and in 1 case the latter was used exclusively. Considerable improvement was noted with a dose of 300 mg. daily. Ratschow³ treated 2 patients having parkinsonism, using a maximum dose of 800 mg. daily in 1 case. He reported tremor and rigidity in 1 patient as having been completely relieved. There does not seem to have been any intensive study of a series of cases for prolonged periods of time.

In considering the effectiveness of any form of therapy for parkinsonism it is necessary to emphasize a difficulty inherent in any clinical evaluation of improvement since it is well known that this may be influenced greatly by subjective alterations in the condition of the patient. If one observes our results as shown in Table 1, it immediately becomes clear that in no instance has syntropan been beneficial in relieving the symptoms until the dose has reached a level of about 1200 mg. daily. Therefore, there is reason to question the reports in the literature indicating good results with much smaller doses.

A critical examination of our results discloses that in 5 cases no improvement was obtained. In 2 of these (Cases 1 and 2) satisfactory coöperation was not obtained due to the rather prolonged relapses which resulted early in our investigation. This could not be avoided at that time because of the necessity for care in determining possible limitations upon dosage. Another difficulty encountered in the early stage of this investigation was the resistance of patients due to their fear of the large number of tablets required in order to give some of the larger doses. This is readily seen when one considers that a dose of 2400 mg. daily is equivalent to 48 of the standard 50 mg. tablets available on the market. This difficulty was later circumvented through the use of specially produced 200 mg. tablets. The third case (Case 3) showing no improvement was considered as representing an advanced case of idiopathic paralysis agitans. It is the only non-encephalitic case in this series. The other 2 (Cases 11 and 12) showing no improvement exhibited toxic manifestations with relatively small doses. It is interesting to note that in both it was chiefly gastric symptoms which necessitated the withdrawal of syntropan.

In 11 patients a varying degree of improvement was observed. Excessive salivation was effectively controlled in all cases and was never accompanied by dryness no matter how high the dose of syntropan. This beneficial effect upon salivation was usually the first sign of improvement and was manifested with doses of about 1000 mg. daily. The diminution of rigidity and of tremor as evidences of improvement were noted with doses approximating

1200 mg. daily and maximum benefits were obtained with doses of about 2400 mg. daily. This improvement was sufficient in 4 cases (Cases 4, 5, 10 and 13) to enable the patients to walk without previously needed support. One of these patients was able to visit the clinic unaccompanied. In 1 patient (Case 9) the alleviation of rigidity and tremor failed to equal the effectiveness of atropine in these respects; in 1 (Case 13) syntropan was more effective than atropine. This patient had been forced to give up atropine because of toxic symptoms and found much relief in syntropan. Her rigidity was decreased, salivation was improved, and walking was better. In another instance (Case 14) a patient who had received very good effects from atropine was forced to give up the drug because of bladder disturbances. On 2400 mg. of syntropan he was able to parallel fully the effects of atropine and experienced no trouble with his bladder.

Involuntary closing of the eyes which was a troublesome symptom in 2 patients (Cases 7 and 8) did not respond to syntropan. In 1 patient (Case 10) the frequent occurrence of oculogyric crises was a conspicuous feature of parkinsonism. This patient while receiving syntropan showed a reduction in frequency from three times weekly to once in 2 weeks. Syntropan showed slight if any beneficial effect upon the stuttering speech defects existing in 2 patients (Cases 4 and 7).

The effectiveness of syntropan was conclusively demonstrated in 2 patients (Cases 6 and 8) who, after the appearance of toxic symptoms, allowed withdrawal of syntropan without immediate replacement by other medication. In these cases an exacerbation of parkinsonian features such as salivation, tremor and rigidity occurred within 48 hours after cessation of syntropan therapy. A similar exacerbation of symptoms was observed in 1 other patient (Case 7) and was later explained by the information that the patient had spontaneously decided to stop taking syntropan.

That toxic manifestation may result from the administration of syntropan is obvious (Table 1). The relative character, frequency and intensity of toxic symptoms when compared with other remedies, particularly atropine, deserves careful consideration. It is evident that blurred vision, flushed face and dryness of mouth, which regularly result from atropine or stramonium medication did not occur with syntropan therapy until the dose of 3200 mg. was reached, when mild blurring of vision was noted in 2 cases (Cases 6 and 8). This is in striking contrast to the early appearance of these troublesome symptoms when atropine is given. Bowel or bladder dysfunctions were not noted in any of the cases receiving syntropan. This contrasts with the not infrequent toxic symptom of dysuria due to atropine. Gastric symptoms in the form of nausea and vomiting necessitated the early withdrawal of syntropan

TABLE 1.—RESULTS OF SYNTROPAN THERAPY.

No.	Case.	Sex.	Age.	Acute enceph.	Parkinsonism.		Syntropan therapy.				Remarks.
					Dura- tion, yrs.	Intensiv- ity.	Dura- tion.	Result.	Maxi- mum dose, mg.	Toxic symptoms.	
1	C.C.	F	32	No	3	Moderate	2 wks.	0	1200	None	Terminated during relapse with oculogyric crises and sadism
2	E.B.	F	40	Yes	14	Moderate	3 wks.	0	1400	None	Terminated during relapse with increased tremor and salivation
3	E.B.	F	53	No	6	Marked	5 wks.	0	1600	None	Idiopathic paralysis agitans
4	H.G.	M	50	Yes	11	Marked	4 wks.	+	2400	Palpitation; vertigo	Spontaneous cessation; uncoöperative
5	J.M.	M	54	Yes	8	Marked	5 mos.	+	2400	Transient palpitation	Normal E.K.G.
6	R.R.	F	31	Yes	9	Mild	5 mos.	+	3200	"Light-headed"; confusion; blurred vision; nausea; vertigo	Increased tremor during period without syntropan; normal E.K.G.
7	C.Z.	M	29	No	7	Moderate	5 mos.	+	3200	Sluggish; drowsy; "fog"; visual hallucinations	Increased rigidity and salivation after withdrawal of syntropan; normal E.K.G.
8	J.H.	M	33	Yes	3	Mild	7 mos.	+	3200	Episodic "trances" with blurring, palpitation and sense of impending death	Increased rigidity and salivation after withdrawal of syntropan
9	E.F.	F	33	Yes	11	Marked	3 wks.	+	3200	None	Atropine more effective for rigidity Oculogyric crises less frequent with syntropan; normal E.K.G.
10	E.L.	M	19	?	5	Marked	5 wks.	+	3200	None	
11	M.E.	F	27	No	1/2	Mild	10 dys.	0	1600	Nausea; vomiting	Same result on 2 occasions Much improved
12	H.R.	F	26	No	6	Marked	1 wk.	0	1000	Nausea; vomiting; vertigo	
13	A.B.	F	55	No	2	Marked	3 mos.	+	1200	None	Much improved
14	R.L.	M	60	No	6	Moderate	4 mos.	+	2400	None	
15	V.W.	F	47	No	4	Marked	4 mos.	+	2000	Weakness	Much improved
16	M.Z.	F	68	No	20	Marked	6 mos.	+	1600	None	

in 2 patients (Cases 11 and 12). In 2 of the 8 patients receiving 2400 mg. daily palpitation appeared. It was a transient symptom in 1 (Case 5) while in the other (Case 4), combined with vertigo, it caused spontaneous cessation of syntropan therapy. Repeated electrocardiograms in 4 cases revealed no abnormalities.

During this study 5 patients were given syntropan in doses as high as 3200 mg. daily. Of these patients 3 showed more alarming toxic symptoms than any noted previously. They were chiefly referable to the nervous system and consisted of confusion, sluggishness, drowsiness and "trance"-like episodes in which a sense of impending death was experienced. One patient (Case 7) complained of quite vivid visual hallucinations.

Because of the occurrence of alarming toxic symptoms and because of the failure to show further improvement with doses exceeding 2400 mg. daily, this has been considered the maximum therapeutic dose of syntropan for the treatment of parkinsonism. Therefore, of the 14 patients in this series who were potentially capable of reaching this therapeutic dose there were 3 (Cases 4, 11 and 12) in which toxic manifestations were sufficient to prevent effective therapy. In 10 patients mild or moderate symptomatic relief was obtained. From these results it would seem that syntropan is definitely useful in many of those cases where atropine cannot be administered because of toxic symptoms. Syntropan may also prove to be the remedy of choice in early cases of parkinsonism where the regularly associated by-effects of atropine would be most annoying and possibly incapacitating.

The use of syntropan in conjunction with the other drugs used in the treatment of parkinsonism has not been investigated as yet. This would appear to be advisable, especially in view of the fact that one of the most striking therapeutic differences between atropine and syntropan is the subjective sense of well-being experienced by the patient receiving the former remedy.

Summary and Conclusions. A group of 16 patients having parkinsonism have been treated by means of syntropan. The maximum therapeutic dose has been determined and is considered to be 2400 mg. daily. Of 14 patients who were potentially capable of reaching this dose, in 10 (71%) mild or moderate symptomatic relief was obtained without the development of any toxic manifestations. From these results it would appear that syntropan is definitely useful in many of those cases where atropine cannot be administered because of the frequently associated toxic symptoms.

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PELLAGRA AND PORPHYRINURIA.

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GROSS pellagra occurs most commonly in warm, sunny climates. In its classic and severe form, the disease begins to appear in the late spring and reaches its peak at the height of summer. The typical dermatitis of pellagra is usually most evident over the exposed parts of the body, and when it is present, there is almost always a definite history of prolonged exposure to sunlight. Because of this evident influence of solar irradiation, various photodynamic hypotheses have been advanced to explain the genesis not only of such skin lesions, but even of pellagra.¹¹

Among the chemical agents which are known to be capable of inducing photosensitivity, the porphyrins have received a good deal of attention in recent literature. The injection of porphyrin into man⁹ and animals⁷ results in photosensitivity. Furthermore, it is known that patients suffering from porphyria, if exposed to the sun, develop symmetrical skin lesions which have been compared to pellagrous dermatitis.^{1,8} In recent years it has been suggested by several authors^{6,8,16} that pellagrous dermatitis may result from the effect of sunlight on skin that has been sensitized by porphyrin. In apparent support of this hypothesis Beckh, Ellinger and Spies² reported the presence of excessive amounts of porphyrin in the urine of 14 cases of "alcoholic" pellagra and subsequently, Spies and his associates have recorded on several occasions^{12,14,15} the presence of porphyrin or "porphyrin-like" substances¹³ in the urine of pellagrins. As a result of these reports it is now widely held that an increased excretion of porphyrin in the urine is a characteristic feature of pellagra.

Unfortunately this belief is due to the dissemination of an erroneous interpretation of the test used by Beckh, Ellinger and Spies. Dobriner and Rhoads⁴ have suggested that the simple test which Spies and his associates employed for the detection of porphyrin in the urine is quite non-specific. Watson^{17b} and the present authors¹⁰ have more recently demonstrated that the color reaction obtained in this test is due to the presence of "urorosein" in the urine, a

pigment which does not resemble porphyrin or porphyrin-like substances in any way.

Dobriner and his collaborators⁵ and Watson^{17a} have shown that porphyrin in increased amounts may occur in the urine of alcoholic pellagrins. But the present authors observed an increased excretion of porphyrin in the urine of "alcoholic" patients both with and without pellagra, while no increase in porphyrin was observed in random specimens of urine from 4 cases of endemic pellagra unassociated with alcoholism.* However these urine samples were shipped from a distance and the porphyrin may have decomposed in transit.¹⁰

In the following communication some observations are reported on 6 pellagrins in whom no increased excretion of ether-soluble porphyrin was detectable in the urine during their stay in the hospital. A seventh pellagrin excreted a large amount of porphyrin during his first admission to hospital, but on a second admission he presented no porphyrinuria.

The clinical criteria for the diagnosis of pellagra in these patients are given in Table 1. Three of the patients studied gave no history of alcoholism, while the other 4 had partaken of large amounts of alcohol over a considerable period previous to their admission to hospital. So far as could be judged from the history given by all 7 patients, their diet had been deficient in protein, fresh fruits and vegetables.

Methods. All patients (with the exception of Case 5) on their admission to hospital were placed at bed rest, and given a standard 3000 calorie diet containing only small amounts of the water-soluble vitamins; Case 5 was given a ward diet.

Twenty-four-hour specimens of the urine from these patients were collected in brown bottles under toluene and were examined for ether-soluble porphyrins by a modification of the quantitative fluorometric method of Brugsch and Keys,³ details of which are given below. In 4 patients (Cases 1, 2, 3 and 6) porphyrin excretion studies were continued throughout their stay in hospital. In the remainder, urinary porphyrin studies were made during the first 3 days following their admission to hospital.

The Estimation of Ether-soluble Porphyrin in the Urine. Fifty milliliters of urine acidified with 10 ml. of glacial acetic acid are extracted with 200 ml. ether in $\frac{1}{2}$ liter brown glass bottle, revolving at between 50 and 100 times per minute on a rotary shaking machine in a dark room, for 4 hours. The ether layer is then removed in a separatory funnel. The urine is again extracted on the machine for a further 30 minutes with 100 ml. fresh ether, and the two ether extracts combined in the separatory funnel. Emulsions, when present, are broken down by the addition of a few drops of caprylic alcohol or glacial acetic acid to the ether extract. Care must be taken not to lose any of the emulsion during separation since it may contain a large amount of the extracted porphyrin.

The ether is then washed 6 times with distilled water and all water is drawn off about 5 minutes after the final washing. Five or 10 ml. 5% hydrochloric acid solution (by volume) is added to the ether, and the mixture is rotated on the machine for fifteen minutes. Porphyrin passes from the ether phase into the hydrochloric acid and this solution, if porphy-

* The urine was obtained through the courtesy of Dr. Tom D. Spies.

rin is present, gives a bright red fluorescence when examined in front of an ultraviolet light source in a dark room.* Extraction of the ether layer with small amounts of hydrochloric acid is repeated until the hydrochloric acid extracts show no further fluorescence.

The hydrochloric acid extracts are combined and made up to a suitable volume, usually 20 ml., by the addition of more dilute hydrochloric acid solution. A small amount of the total acid extract is taken and made up to 10 ml. with 5% hydrochloric acid and its fluorescent intensity is compared in front of the ultraviolet light source with two standard solutions of coproporphyrin I, containing 0.5 micrograms of coproporphyrin I in 10 ml. 5% hydrochloric acid and 1 microgram of coproporphyrin I in 10 ml. 5% hydrochloric acid, respectively. The unknown hydrochloric acid solution must be adjusted so that its fluorescent intensity can be read between the fluorescent intensities of the two standard tubes. Care must be taken to have solutions in nonfluorescent glass tubes of equal dimension and to compare the fluorescent intensity at the meniscus of the solutions and not that of the whole tube.

If large amounts of porphyrin are present, chloroform extraction of the hydrochloric acid phase must be made in order to remove any chloroform-soluble porphyrins which may be present. The presence of porphyrin can be verified by use of a direct vision spectroscope, only if large amounts of porphyrin are excreted. The *per diem* excretion of porphyrin in the urine can be calculated by using the following equation:

$$\frac{\text{Total 24-hour urinary volume}}{\text{Volume of urine extracted}} \times \frac{\text{Final volume of hydrochloric acid extract}}{\text{Volume of hydrochloric acid extract used for reading against standard}} \times \text{reading in micrograms} = \text{daily excretion of porphyrin in micrograms.}$$

By this method an excretion of 90 micrograms of porphyrin in 24 hours is the upper limit of normality. The usual 24-hour excretion in normal subjects rarely exceeds 40 micrograms.

The daily urinary porphyrin excretion in the 7 pellagrins during their first 3 days in hospital, with 1 exception (Case 7, first admission), was never above the upper limit of normality (Table 1). Furthermore, the 4 patients upon whom studies were made throughout their hospital stay, continued to excrete normal amounts of the pigment, despite the continuance of a diet deficient in water-soluble vitamins. Case 7, a patient with "alcoholic" pellagra, is of special interest since he showed a marked porphyrinuria together with an increased fecal porphyrin excretion only during the first of his two admissions to hospital, though on both admissions there was a marked symmetrical dermatitis.

His case history is given briefly below:

CASE 7.—(B. C. H. 954507.) A 65-year-old, white, unemployed plasterer, was admitted to the Boston City Hospital on May 18, 1939, for "soreness" of his hands. During the 5 months preceding his entry to hospital he had been taking at least $\frac{1}{2}$ pint of whisky daily; his meals had been irregular and consisted mainly of coffee, doughnuts, soup and bread; occasionally he had some stew or sausage. In March, 1939, he began to "hang about" out of doors in Franklin Field, Boston, and 6 weeks prior to entry noticed that his hands were becoming sunburnt. This became sufficiently severe

* The ultra-violet light source was Mercury Vapor Lamp No. 87273 and 85267, Central Scientific Company, Chicago, Ill.

to bring him to hospital where he reported that several of his friends at Franklin Field were similarly affected.

Physical examination revealed a well-developed but poorly-nourished male, with evidence of florid pellagra. The skin over the dorsum of his hands and wrists and on his face was thickened and desquamating, leaving

TABLE 1.—THE DAILY EXCRETION OF URINARY PORPHYRIN IN PATIENTS WITH PELLAGRA.

Patient.	Sex.	Age.	Clinical diagnosis.	Clinical findings on admission to hospital.	Urinary porphyrin excretion in micrograms per 24 hours using patient's first 3 days in hosp.	Exposure to sunlight prior to admission.
1 (961089) (B.C.H.)	M	41	"Alcoholic" pellagra	Symmetrical pigmentation of back of hands, wrists and face with scaling and hyperkeratosis Red tongue Cheilosis Diarrhea "Nervousness"	40 40 45	Prolonged
2 (948746) (B.C.H.)	M	39	"Alcoholic" pellagra	Symmetrical dermatitis of back of hands, wrists and face "Collar of Casal" Diarrhea Sore tongue Perleche and cheilosis Anemia	30 25 30	Prolonged
3 (945485) (B.C.H.)	F	65	Pellagra	Emaciation Mild dementia Dermatitis of hands, wrists, face, ankles and antecubital fossæ Vulvitis Perineal inflammation Perleche, red and sore tongue Sialorrhea Diarrhea Anemia	30 10 15	Prolonged
4 (947892) (B.C.H.)	M	49	"Alcoholic" pellagra	Dermatitis of hands and wrists Hyperkeratosis of the elbows Perleche Papillary atrophy of tongue Macrocytosis of the red blood cells without anemia	30 35 30	Prolonged
5 (961416) (B.C.H.)	F	52	Pellagra	Acute dementia Hyperkeratosis of elbows Vulvitis and perineal inflammation Slight sore tongue Pigmentation of hands Neuritis Edema	70 20 25	No exposure
6 (952856) (B.C.H.)	M	47	Pellagra	Symmetrical dermatitis of hands, wrists, neck and ears Diarrhea Perleche Neuritis	70 35 30	Prolonged
7 (954507) (B.C.H.)	M	64	"Alcoholic" pellagra	FIRST ADMISSION—Symmetrical der- matitis of hands, wrists, elbows and face Cheilosis Polyposis of the stomach SECOND ADMISSION—Symmetrical dermatitis of hands, wrists, el- bows, face and neck Red tongue Perleche Cheilosis Diarrhea Neuritis Anemia Irritability	140 110 110 10 15 20	Prolonged

raw, red areas which oozed serum and bled easily. There was also a copper-colored pigmentation extending up the extensor surfaces of his forearm which, like the other skin lesion, was sharply demarcated and symmetrical. His elbows were reddened and the skin overlying them markedly hyperkeratotic. His lips were swollen, cracked and sore. Further study revealed a moderate anemia and complete achlorhydria. Polyposis of the stomach was diagnosed radiologically and the diagnosis was confirmed by gastroscopy. Because of this he was seen by a surgical colleague in consultation. However, operation was not deemed advisable. He was placed in bed on a high-calorie diet containing only traces of the water-soluble vitamins.

During his first 6 days in the hospital, the excretions of ether-soluble porphyrins were increased, not only in his urine (Table 1) but also in his stools, which contained 600 micrograms *per diem* during his first 3 days in the hospital and 375 micrograms *per diem* during the next 3 days (normal output 180 to 250 micrograms *per diem*). From this time onward the porphyrin excretion was within normal limits despite exposure to sunlight for 1 hour each day. During his last 4 weeks in the hospital he was placed on a high-vitamin diet, supplemented with yeast and intramuscular liver injections. He was then discharged, apparently cured, with instructions to report to the hospital for further treatment.

On September 14, 1939, he was again admitted to hospital for recurrence of pellagra. He had not attended the follow-up clinic and had returned to his former habits, drinking large quantities of alcohol and sitting in the sun in Franklin Field. His condition was much more marked than during his previous illness. He had a severe, watery diarrhea; his hands, face and neck showed a more marked dermatitis; his lips were cracked, and there were fissures at the corners of his mouth and behind his ears; his tongue was red and there were objective signs of neuritis of the lower limbs. He was extremely irritable and complained bitterly of insomnia. He had a moderate anemia with macrocytosis. Gastric polyposis was present on Roentgen ray examination. He was again placed at bed rest, on a high-calorie diet containing only traces of the water-soluble vitamins. Studies on his porphyrin excretion showed a normal output of urinary porphyrin, which did not at any time reach an abnormal level.

Conclusions. The evidence presented here would suggest that while alcoholic pellagrins occasionally exhibit an increased excretion of ether-soluble porphyrin, this porphyrinuria is by no means a constant finding and bears no relationship, at least in the cases reported in this communication, to pellagrous dermatitis or to prolonged exposure to sunlight. Furthermore, no increase in porphyrin excretion was found in the 3 patients reported here who gave no history of alcoholism, nor in the 4 patients with endemic pellagra included in a previous communication.¹⁰ It must, therefore, be concluded that an increased excretion of porphyrin in the urine is not an essential feature of pellagra and, it seems probable, that when porphyrinuria appears in pellagra, it is perhaps consequent upon some alteration of liver function, as Dobriner⁵ has suggested. Finally, we wish to stress that an examination of the urine for increased porphyrin does not in any way aid in the diagnosis of pellagra.

We wish to thank Dr. K. Dobriner for his suggestions in regard to the technique employed; Mr. Frank Cohen, M.S., for excellent technical assistance; and Dr. William B. Castle for his advice and helpful criticism in the preparation of this paper.

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RENAL FUNCTION IN LATE TOXEMIA OF PREGNANCY.

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MANY attempts have been made to demonstrate some characteristic abnormality of renal function in late toxemia of pregnancy which might serve as an aid in diagnosis, or a gauge of prognosis and treatment. Tests of the ability to concentrate urine, examinations of urinary sediment, estimations of the rate of excretion of phenolsulphophthalein (phenol red) and determinations of urea clearance have alike failed to establish the presence of abnormalities which might systematically be correlated with the clinical state (Hurwitz and Ohler,¹⁸ Elden and Cooney,¹¹ Dieckmann,¹⁰ Elden, Sinclair and Rogers,¹² Brown,³ Chesley⁵). Estimations of renal blood flow determined from plasma diodrast clearance have yielded similar results (Chesley *et al.*⁷).

Proteinuria which occurs during late toxemia of pregnancy is evidence of the constant presence of a renal and, more particularly, of a glomerular lesion, although neither its presence nor severity of themselves aid greatly in prognosis. It is therefore apparent that a test of renal function which might yield more definite results in toxemia of pregnancy than those previously used must concern itself with the measurement of glomerular function. The establishment of inulin clearance as a measure of glomerular filtration and of diodrast and phenol red clearances as measures of renal blood flow in work furthered and reviewed by Smith²² has yielded methods which might properly be applied to this problem. We have therefore used these methods in observations of renal function in cases of late toxemia of pregnancy.

Methods. 1. *Selection of Patients.* The cases studied were selected from those seen in the wards of the Obstetrical Service of the Indianapolis City Hospital. The syndrome of late toxemia of pregnancy was evidenced by hypertension, edema and proteinuria in nearly all of them. Both edema and marked proteinuria were absent in a few instances. Many of them complained of headache and visual disturbances. Eclampsia developed in 9 cases, in 2 of which the convulsions appeared postpartum. Because particular interest was paid the typical syndrome as it appeared in young primiparae, the distribution of cases as to age and parity does not reflect the frequency with which the various types of cases were admitted to the wards for treatment.

Patients whose edema was slight, whose retinal changes were few, whose arterial hypertension fell with rest in bed, who had few subjective symptoms and no convulsions, were considered instances of mild toxemia. Cases with greatly increased diastolic arterial pressure, severe proteinuria, marked alterations of the ocular fundus, and who developed convulsions, were considered severe.

2. *Tests of Renal Function.* Renal function was measured by means of the renal clearances of phenol red and inulin, supplemented in some cases by simultaneous observations of the clearances of diodrast and urea. The preparation and administration of infusion fluids, collection of specimens and calculation of results was in general done by the methods described by Smith, Goldring and Chasis.²³ Phenol red was determined by the method outlined by Corcoran and Page,^{8a} inulin by the method of Corcoran and Page,^{8b} diodrast by a slight modification of the method of White and Rolf²⁷ and urea by the manometric hypobromite method of Van Slyke and Kugel.²⁵ Urine flow was not accurately measured, since the calculation of excretion rate was made from the volume of combined urine and washings. However, care was taken to maintain the rate of urine formation above 0.5 cc. per minute.

3. *Calculation and Interpretation of Results.* At low plasma levels the proportion of diodrast removed from blood plasma as it passes through the normal explanted dog's kidney varies from about 74% (White and Heinbecker²⁶) to 85% (Corcoran, Smith, and Page⁹). It may be assumed that some blood passes to non-excretory tissues, so that the extraction of diodrast by excretory tissues is probably greater than 85%. Further, there is a small renal contribution of diodrast from the red cells (White and Heinbecker²⁶). The net diodrast excretion is therefore, approximately equal to complete extraction from plasma, and (DC) (plasma clearance of diodrast) is nearly equal to the rate of plasma flow to excretory renal tissue (effective renal plasma flow). The value $\left(\frac{DC}{1 - \text{hematocrit}} \right)$ may therefore be accepted as a close approximation of the rate of effective renal blood flow (R.B.F.) (Smith, Goldring and Chasis²³). Calculated in this manner, the renal blood flow of normal adult males averages about 1300 cc. per 1.73 sq. m. of body surface per minute (range 1050 to 1680 cc. per 1.73 sq. m. per min.) (Chasis, Ranges, Goldring and Smith⁴). The renal blood flow of normal pregnant and non-pregnant women, calculated from plasma diodrast clearance, averages 856 cc. per 1.73 sq. m. of body surface per minute (range 694 to 1235 cc. per 1.73 sq. m. per min.) (Chesley and Chesley⁶).

Phenol red is removed from plasma by the secretory mechanism also responsible for excretion of diodrast. However, the proportion of phenol red removed from plasma by the explanted dog's kidney averages only 48.5% (Corcoran and Page^{8a}). The plasma clearance of phenol red (PC) in dogs is therefore a little more than one-half that of diodrast. In human beings, the ratio of simultaneous phenol red/diodrast clearance $\left(\frac{PC}{DC} \right)$ aver-

ages 0.56 (Smith, Goldring and Chasis²³). The clearance of phenol red is depressed about 5% by the presence of small concentration of diodrast (1 mg. per 100 cc.). Consequently, the value $\left(\frac{PC}{0.6}\right)$ will nearly equal the average level of plasma diodrast clearance and this value divided by the plasma fraction (1-hematocrit ratio) indicates the approximate level of effective renal blood flow. The phenol red clearance of normal males averages 394 cc. per minute per 1.73 sq. m. of body surface (Smith, Goldring and Chasis²³). Renal blood flow calculated as $\left(\frac{PC}{0.6}/1\text{-hematocrit}\right)$ averages 1125 cc. per 1.73 sq. m. of body surface per minute.

Inulin is excreted only by glomerular filtration (Smith²²). Inulin clearance (IC) is therefore an exact measure of the volume of glomerular filtrate. Plasma diodrast clearance is nearly equal to the rate of plasma flow through excretory renal tissues. Plasma phenol red clearance equals approximately 60% of this value; consequently, the ratios IC/DC or $\frac{IC}{PC/0.6}$ express the proportional volume of glomerular filtrate formed from plasma as it perfuses the kidneys. This value, known as filtration fraction (FF), varies with changes of intraglomerular pressure and, independently of these, with alterations in the efficiency of the filtering surface. Increased intraglomerular pressure is reflected in an increase of filtration fraction since the proportion of water removed by filtration is increased. Swelling of the filtering surface would lower filtration fraction and decrease the removal of plasma water by impairing the efficiency of the filter. The filtration fraction of normal adult males averages 0.177 (range 0.153 to 0.218) (Chasis, Ranges, Goldring and Smith⁴). The ratio $\left(\frac{PC}{IC}\right)$ is similarly a measure of the relative volume of water removed from renal plasma by filtration. The average ratio of phenol red/inulin clearance $\left(\frac{PC}{IC}\right)$ in normal males is 3.2. (Smith, Goldring and Chasis²³).

The values reported here are: 1, renal blood flow (RBF) either as calculated from plasma diodrast clearance, or as approximated from plasma phenol red clearance; 2, plasma diodrast clearance in some cases (DC); 3, plasma phenol red clearance (PC) without correction for the presence of diodrast; 4, plasma inulin clearance (IC); 5, filtration fraction (FF) either as calculated from the ratio $\left(\frac{IC}{DC}\right)$ or as approximated from phenol red and inulin clearances; 6, phenol red/inulin clearance ratio $\left(\frac{PC}{IC}\right)$ in those cases in which diodrast clearance was not done. Urea clearance was determined in all patients; in some of them simultaneously with the clearances of phenol red and inulin.

4. *Other Observations.* Estimations of plasma protein content were made in most cases. Addis concentration test and counts of the organized urinary sediment were done in some cases.

Results. I. INITIAL OBSERVATIONS. The initial observations of renal function fall into three groups: A, one in which glomerular filtration is depressed out of proportion to the rate of renal blood flow (low FF or high $\frac{PC}{IC}$); B, a group in which the relative volume of glomerular filtrate is increased (high FF, low $\frac{PC}{IC}$); C, a group in which both FF and the ratio $\frac{PC}{IC}$ are within the normal range.

GROUP B. *High Filtration Fraction.*

1	6	M	2	0	160/110 (660)	..	250	96	..	(0.230)	2.6	..	10A
Family history of hypertension.													
2	7	M	1	0	154/110 (768)	..	345	143	..	(0.248)	2.41	6.6	35A
3	8	M	1	0	140/100 (890)	..	338	136	..	(0.241)	2.48	5.8	4A
					138/84 (770)	..	309	127	..	(0.247)	2.42	..	10P
					110/64 972	573	(336)	95	..	0.165	..	7.4	40SP
Family history of hypertension.													
4	4	M	7	0	150/120 (860)	..	323	137	76	(0.254)	2.36	6.2	4A
					160/104 (707)	..	250	113	88	(0.272)	2.21	..	10P
					170/105 (685)	..	252	104	68	(0.249)	2.42	..	73P
					168/108	422P
Symptoms of hypertension for about 10 years.													
5	6	M	8	0	230/140 (664)	..	262	111	..	(0.254)	2.35	7.8	10P
Hypertension present before onset of this pregnancy.													
6	8	M	1	0	145/100 (432)	..	161	62	..	(0.230)	2.57	..	7A
Hypertension present before onset of this pregnancy.													
7	7	M	1	0	155/100 (773)	..	288	115	..	(0.249)	2.45	7.9	7A
Second pregnancy 1 year later without hypertension.													
8	8	M	1	P1	136/92 (465)	..	173	79	..	(0.274)	2.20	..	10P

GROUP C. *Normal Filtration Fraction.*

1	8	M	1	P1	152/90 (1175)	..	440	134	..	(0.183)	3.29	6.7	5A
2	7	M	1	0	164/104 (830)	..	331	112	79	(0.203)	2.95	6.9	40A
					124/74 907	625	(331)	126	..	0.203	..	6.8	390P
Second observation at term of normal pregnancy.													
3	8	M	1	0	168/102 (590)	..	215	74	..	(0.206)	2.90	6.9	4P
4	8	M	1	0	144/90 (700)	..	260	88	62	(0.203)	2.95	6.4	23A
					130/80 988	592	342	125	..	0.211	595P
5	7	M	6	0	170/105 (1162)	..	424	145	..	(0.192)	2.92	6.8	4A
					140/80 (914)	..	327	115	..	(0.206)	2.84	..	2SP
					144/68 623	458	(275)	117	..	0.256	381P
6	7	M	1	0	190/110 (810)	..	320	105	69	(0.197)	3.05	..	5P
7	8	M	1	0	150/100 (699)	..	256	77	..	(0.181)	3.32	..	3A

The abbreviations RBF, DC, PC, IC and UC indicate respectively renal blood flow, plasma diodrast clearance, plasma phenol red clearance, plasma inulin clearance and plasma urea clearance. These values are expressed in cc. per 1.73 square meters of body surface per minute. Renal blood flow calculated from phenol red clearance is indicated by parentheses. FF indicates filtration fraction derived from the inulin/diodrast clearance ratio; those calculated from phenol red clearance are in parentheses. Phenol red/inulin clearance ratio (P/I) is calculated only in those cases in which diodrast was not administered. No correction is made in phenol red clearance for depression by diodrast. Phenol red clearances observed during administration of diodrast are therefore indicated by parentheses. The day on which the observation was made is indicated in number of days ante- or postpartum.

Seven of the 13 cases were considered severe, and antepartum eclampsia was present in all of these. Total plasma protein content was decreased below 6.5 gm. per 100 cc. in the 11 cases in which this determination was made. There was marked proteinuria in every instance. Constriction of retinal arterioles was present in 12 cases and retinal edema or papilledema in 6. Retinal hemorrhages and exudates occurred in 2 instances.

Group B. The average approximate renal blood flow during the initial examination was 688 cc. per 1.73 sq. m. per minute. The approximate average filtration fraction was 0.247. The ratio $\frac{PC}{IC}$ was decreased in all cases. Three of these patients had shown

arterial hypertension before the pregnancy during which observations were made. Three others of this group stated that hypertension was present in other members of their family. Plasma protein content was greater than 6.5 gm. per 100 cc. in 3 of 5 cases in which it was determined. The fundi were normal in 1, showed moderate constriction of retinal arterioles in 2, constriction and sclerosis in 3 and constriction, sclerosis and scattered small retinal hemorrhages in 1. Proteinuria was scant (trace) in 3 cases. A postpartum convulsion occurred in 1 case.

Group C. In the third group of 8 patients, renal blood flow averaged 853 cc. per 1.73 sq. m. per minute. The approximate average filtration fraction was 0.165. The average ratio $\frac{PC}{IC}$ was

3.05. Retinal arterioles were slightly constricted in 1 instance. The retina appeared to be edematous in 2 cases. Peripheral edema was slight and proteinuria moderate. Total plasma protein content was greater than 6.5 gm. per 100 cc. in all but 1 of 5 cases. All were regarded as mild cases of late toxemia of pregnancy, but 1 had a mild postpartum convulsion. One of them (Case 2) was reexamined at term of a second pregnancy, which was completed without evidences of toxemia. The results at the second examination are nearly identical with those of the first observation.

II. SUBSEQUENT COURSE. 1. *Immediately Postpartum.* Group A. Although filtration fraction was decreased in 1 case on the eighth day postpartum, this abnormality had disappeared by the fifth day in another. Filtration had increased in all cases of the first group at the time of second observation. Renal blood flow fell from the high level obtained at first observation in 8 cases of this group, while it increased greatly in the 1 case in which it had been very low (Case 7). In some of these cases the blood pressure had not yet returned to normal at the time at which these changes were observed.

Groups B and C. Observations shortly after delivery in patients of these groups are too scant to allow conclusions. No change of blood flow or filtration fraction had occurred after delivery in Cases 3 and 4 (Group B) and Case 5 (Group C).

2. *Later Course.* Group A. Arterial hypertension with decreased renal blood flow and increased filtration fraction persisted in the 1 case of the first group in which late toxemia of pregnancy complicated the course of essential hypertension (Case 13). Three (Cases 1, 8 and 10) of this group have developed slight arterial hypertension with decreased renal blood flow and some increase of filtration fraction. Case 7 may be entering a similar phase. Blood pressure observations during pregnancy, but before the onset of toxemia were within normal limits in these cases. Three patients (Cases 3, 4 and 12) show a tendency to increased filtration fraction and decrease of renal blood flow, but without hypertension. One of these (Case 3) was delivered of a normal full-term pregnancy 6 months before the last observation. Three patients (Cases 2, 6 and 7) have

normal blood pressures, renal blood flows and filtration fractions when observed from 4 months to a year postpartum. Cases 5 and 11 yielded normal values when seen 2 and 4 weeks postpartum, but are no longer under observation.

Group B. Of the cases of the second group, 1 which had shown hypertension for about 10 years before symptoms of toxemia developed, continues to show hypertension, decreased renal blood flow and increased filtration fraction (Case 4). There was no evidence of hypertension nor of renal abnormality in another (Case 3) observed more than a year after toxemia. This patient had previously shown no hypertension. One (Case 7) went through a second normal pregnancy 1 year after the toxemia. Moderate hypertension has persisted in Cases 5 and 6, although observations of renal function are lacking.

Group C. Many members of the third group are similarly unavailable for reëxamination. One of them (Case 2) at term of a second normal pregnancy shows almost exactly the same rate of renal blood flow and filtration rate which were present during her first mildly toxemic pregnancy. Another (Case 5) now shows slight arterial hypertension, decreased renal blood flow, and increased filtration rate.

Discussion. I. *Filtration Fraction.* The separation of cases of late toxemia of pregnancy into three subgroups in this report is made on differences in filtration fraction. There are also certain differences in the rates of renal blood flow in these groups. Since distinction of these types on the basis of test of renal function is apparently coupled with differences in prognosis, it is pertinent to inquire whether this separation is arbitrary or justifiable.

The ranges of filtration fraction, or the ratio $\frac{PC}{IC}$, found in normal males (Chasis, Ranges, Goldring and Smith,⁴ and Smith, Goldring and Chasis²³) were the criteria used in making this separation. Our own experience (unpublished) from observations in normal and hypertensive females has tended to confirm their results. Observations of filtration fraction estimated from creatinine and diodrast clearances in normal pregnant and non-pregnant females have established that filtration fraction is not altered by pregnancy (Chesley and Chesley⁶). However, since renal clearance of creatinine in human beings is in part normally due to tubular secretion (Smith²²), the absolute values of filtration fraction obtained from determinations of creatinine clearance are not regarded by Chesley and Chesley as strict measures of the proportion of water removed from plasma by filtration. Accurate indications of filtration fraction are only obtainable when inulin clearance is determined. It is therefore likely that the criteria used in the separation of our cases into subgroups at the limits of the ranges of normal filtration are applicable to pregnant women.

Filtration fraction, approximated from simultaneous determina-

tions of endogenous creatinine and diodrast clearances in cases of toxemia of pregnancy by Chesley, Connell *et al.*⁷ were not considered of value by the authors. It should be noted, however, that the range of approximate filtration fraction which they obtained was 0.084 to 0.283 and is therefore in general agreement with our results. Further, by calculation from their results, it will be noted that the average of "filtration fraction" in severe cases and in eclampsia is 0.137, while the average of mild cases is 0.154. This is also consistent with our observations of the greater frequency of low filtration fraction in severe and eclamptic cases. These authors also note that renal blood flow is characteristically normal in toxemia of pregnancy (average 844 cc. per 1.73 sq. m. per min.) although the range of variation is greater than is found in normal pregnant and non-pregnant women. This observation is also in agreement with our data.

We may therefore conclude that late toxemia of pregnancy may, by observations of diodrast or phenol red and inulin clearances, be divided into groups, one with low, another with high, and another with normal filtration fraction.

II. *Renal Lesion.* The changes found in patients of Group A are of particular interest. All showed decreased or low filtration fraction. In many of them the rate of renal blood flow was increased during toxemia over levels which it attained in observations made after delivery, while it was reduced in 1 case, in whom it subsequently increased. The decrease of filtration of water from plasma in these cases was due either to hemodynamic intrarenal changes resulting in decreased intraglomerular pressure (constriction of afferent arterioles or relaxation of efferent arterioles) or to increased resistance of the filtering surface. The slight increase of renal blood flow found in some of these cases is consistent with efferent arteriolar dilatation, although it excludes afferent vasoconstriction. However, it would be impossible on this assumption to explain reduced filtration fraction in those cases in which renal blood flow was normal or decreased. It is therefore likely that the primary functional lesion lies in the glomerular filter, which, even under the increased arterial pressure of late toxemia, fails to permit the passage of the normal fraction of plasma water.

Swelling of the glomerular basement membrane is present in fatal cases of preëclampsia and eclampsia (Bell,² Baird and Dunn⁴) and may be found long after when death has occurred from other causes (Page and Cox¹⁹). This lesion is present even in the early stages of preëclampsia, while other lesions found in fatal late toxemia of pregnancy may be of recent and terminal origin. It is therefore likely that this change is in some measure typical of late toxemia of pregnancy. The reduced efficiency of filtration which we have found in cases of our first group is the functional equivalent of this anatomic change. We therefore consider a reduction of filtration fraction as characteristic of many cases of late toxemia of pregnancy.

Bell,² Peters²¹ and others have described the histologic differences between the kidney in late toxemia and in acute nephritis, while noting that the thickness of the glomerular membrane is increased in both conditions. As in toxemia, a decrease in filtration fraction occurs during acute nephritis in human beings (Goldring and Smith¹⁵) and is also present during the nephrotic stage of chronic glomerulonephritis (personal observation). A similar change occurs as a result of subendothelial glomerular swelling in the course of experimental nephrotoxic nephritis in dogs (Fouts, Corcoran and Page¹³). Renal blood flow is increased during the early acute state of nephrotoxic nephritis in dogs and later usually decreases, apparently as the result of reversible occlusion of the glomerular capillaries by swelling. The low renal blood flow observed initially in Case 8 (Group A) may be similarly explained. Some of these cases whose blood flow was normal and not altered during recovery may also have had areas of glomerular occlusion. The tendency to increased renal blood flow in other cases, confirmed by restoration of renal blood flow at lower levels after recovery, further suggests a similarity of the renal state in toxemia of pregnancy and in nephrotoxic nephritis. We are therefore tempted to suggest that there may be some underlying similarity in the genesis of these processes.

The increased filtration fraction and low renal blood flow present in cases of the second group is similar to the state which obtains in essential hypertension (Goldring, Chasis, Ranges and Smith¹⁶). Constriction of the efferent glomerular arterioles increases intraglomerular pressure, and therefore the proportion of water removed from plasma by filtration, while it restricts the flow of blood through the kidney. Efferent arteriolar constriction in essential hypertension may be the result of the operation of the chemical mediating system described by Page,²⁰ in which angiotonin is the effective renal vasoconstricting agent (Corcoran and Page^{8c}).

The absence of renal functional abnormalities in cases of the third group can at present only be ascribed to the relative mildness of the condition in these cases.

III. *Clinical Correlation.* The diagnosis of late toxemia of pregnancy is entirely descriptive. As Williams²⁸ and Zimmerman and Peters²⁹ have emphasized, the term includes a variety of clinical and pathologic entities. The classification suggested by Goldring¹⁴ is in general accord with other systems of classification and with present knowledge. Slightly modified, this classification includes (A) specific toxemia of pregnancy, with or without convulsions, *i. e.*, preëclampsia and eclampsia of unknown origin; (B) preëxisting or, possibly, latent essential hypertension; (C) chronic or acute glomerulonephritis and pyelonephritis; (D) combinations by superimposition of specific toxemia of pregnancy in cases of the other two groups. This outline does not include the group of "water retention toxemias" due to hypoproteinemia or excessive sodium intake recently described by Strauss.^{24a,b} The existence of these several

types clinically grouped as late toxemia of pregnancy may explain our observation of groups of cases differentiated by filtration fraction.

Cases of our first group were in every way typical of specific late toxemia of pregnancy. Hypertension preëxisted in 1 case, but the renal changes in this case during toxemia were not those of essential hypertension, although they subsequently reverted to this type. Seven of the 13 cases had eclampsia and were regarded as severe on other grounds. Plasma protein content was markedly reduced in some of them. However, it does not appear that hypoproteinemia would reduce filtration fraction, since a decrease of plasma osmotic pressure should, other things being equal, result in increased effective intraglomerular pressure. We therefore do not believe that these patients were primarily cases of "water retention toxemia," although hypoproteinemia may have contributed to their condition. Since we believe that cases of this group were typical of specific toxemia of pregnancy, we suggest that a decrease of filtration fraction is characteristic of this state.

The functional alteration in cases of our second group (Group B) is, as has been noted, identical with that of essential hypertension. It is therefore significant that hypertension was known to be present in 4 of 9 cases before the onset of pregnancy and that 3 other patients of this group had close relatives who either suffer from or died of arterial hypertension. We therefore suggest that patients whose filtration fraction is increased during toxemia of pregnancy suffer from essential hypertension, either preëxisting or formerly latent and whose clinical course is modified by pregnancy.

Clinical manifestations of toxemia were mild in most instances of Group C. Edema was present, but was limited to slight puffiness of the face and early pitting over the shins in all cases. Proteinuria was greater than a trace (1+) in all cases but 1, in which it was recorded as 2+. Retinal arterioles showed some constriction in 5 cases and sclerosis in 1 instance. In 2 patients retinal edema may have been present. Most of these showed marked improvement with rest in bed and general measures of hygiene. The absence of definite abnormalities of renal clearances of phenol red or inulin suggest that renal structural changes were proportionately scant. Consequently, although it appears that these cases more closely resemble those of Group A than those of Group B, we are unable to offer a more definite classification of this group.

IV. *Filtration Fraction in Prognosis.* The data at hand suggest that decreased filtration fraction, whatever the level of renal blood flow, is frequently associated with a severe course and with eclampsia. Filtration fraction is either normal or increased in cases whose courses were mild, although postpartum convulsions occurred in 2 of 20 such patients. Unequivocal statements of the bearing of filtration fraction on prognosis must await a larger series of observations.

Lasting arterial hypertension developed in 3 of 13 cases whose filtration fraction was decreased. Another 3 patients of this group

now show renal changes which may indicate that hypertension will develop. Three at least have recovered without residual hypertension or renal abnormality. The incidence of late hypertension in members of this group is approximately that which might be expected in cases of this type (Herrick¹⁷). Data with regard to late prognosis are inadequate in members of the second and third groups. More definite information as to the statistical influence of filtration fraction on late prognosis will be obtained in continuing observations.

Summary. Observations on the rate of renal blood flow and on the proportion of water removed from plasma by glomerular filtration (filtration fraction) were made in cases of late toxemia of pregnancy.

Filtration fraction was found to be decreased in some, increased in others, and within normal limits in still other cases. Decreased filtration fraction seemed characteristic of those cases which were clinically typical of idiopathic specific late toxemia of pregnancy. Seven of those with decreased filtration were eclamptic. It is suggested that the renal lesion of preëclampsia and eclampsia, namely, swelling of the basement membrane of glomerular capillaries, is functionally expressed in decreased filtration fraction. The similarity of the renal changes in cases of this type and in nephrotoxic nephritis in dogs is noted. The course of toxemia of pregnancy was more severe in cases whose filtration fraction was reduced. Lasting hypertension has since developed in some of these. The persistence of hypertension has been associated with a decrease in renal blood flow and increased filtration fraction, presumably the result of efferent arteriolar constriction.

Clinical observation in patients whose filtration fraction was increased suggest that these suffered from preëxisting or previously latent essential hypertension. No definite classification was made of those cases whose renal blood flow and filtration fraction were within normal limits. The clinical course in both these latter groups was mild.

Conclusions. 1. The characteristic renal lesion of specific late toxemia of pregnancy, namely swelling of the glomerular basement membrane, is functionally expressed in a decrease in the proportion of water removed from plasma by glomerular filtration (filtration fraction).

2. Cases of late toxemia of pregnancy in which filtration fraction is increased, on clinical and functional grounds may be classified as essential hypertension, preëxisting or formerly latent.

3. Cases of late toxemia of pregnancy in which filtration fraction and renal blood flow are within normal limits cannot be classified on renal functional grounds, although many of them are apparently milder expressions of the syndrome of specific late toxemia of pregnancy.

4. The clinical course is more severe and the incidence of eclampsia much greater in those patients whose filtration fraction is decreased.

5. Certain patients who showed decreased filtration fraction during the acute course of toxemia of pregnancy later showed an increase in filtration fraction and a decrease of renal blood flow. Some of these have at the same time developed lasting arterial hypertension.

The authors wish to express their gratitude to the attending staff of the Obstetrical Service, Indianapolis City Hospital, and in particular to Dr. H. F. Beckmann, to the residents on this service, particularly Drs. B. A. Washburn, R. C. Swan, and J. N. Topalgus, and the interns and nurses of this department, to Dr. A. E. Blatt, Messrs. M. L. Garner and Odell Weir of the Lilly Laboratory for Clinical Research, and to Mrs. M. Noel and Mrs. E. Pierce of the Social Service Department of the Indianapolis City Hospital.

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THE ACTION OF PAREDROLINOL AFTER INDUCTION OF HEMORRHAGE AND CIRCULATORY COLLAPSE.

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In a previous study¹ it was reported that paredrolinol sulphate has a beneficial effect in sodium nitrite collapse. Sodium nitrite produces circulatory collapse in the upright position by decreasing the

venous tone, which in turn causes increased venous pooling in the portions of the body below the level of the heart.³ Paredrolinol is useful in this condition because it increases the venous tone.²

Observations were also made on the effect of paredrolinol on the clinical condition, the pulse, and the arterial pressure of 10 patients with advanced circulatory failure (8 from acute infectious diseases, 2 from miliary tuberculosis) characterized by low arterial pressure; rapid, feeble pulse; and cold extremities. In these patients paredrolinol had much less effect than in normal subjects. Although larger doses were used, in only 2 instances did the arterial pressure rise to hypertensive levels. Only 2 of the 10 patients showed definite clinical improvement. It was suggested at that time that this poor response to paredrolinol might be a manifestation of the decrease in total blood volume which is present in certain types of shock, and that paredrolinol, though effective in the circulatory collapse caused by pooling of blood within a dilated venous system (nitrite collapse), might not be helpful in collapse resulting primarily from loss of fluid from the blood stream. Since the clinical picture in critically ill patients is the result of many factors, it is difficult in a given case to ascertain the principal cause of the circulatory collapse, and the reason the response to medication differs from that of normal subjects. In order to determine the effect of a decrease in blood volume on the response of the body to paredrolinol, it was necessary to study under controlled conditions the action of paredrolinol in collapse resulting primarily from decreased blood volume without the complicating factors of infection and tissue damage. The action of paredrolinol on the clinical condition, pulse, and arterial pressure of 6 normal volunteer subjects in whom the blood volume had been decreased by venesection was, therefore, studied. There is no danger in rapidly removing large quantities of blood from normal subjects by venesection. If circulatory collapse occurs, the sharp fall in arterial pressure will prevent the removal of any more blood from the venous system. Normal persons always recover spontaneously from this type of collapse.

Method. The amount of intravenous paredrolinol needed to produce a definite rise in arterial pressure was determined for each subject while in normal state. On the following day from 760 to 1220 cc. of blood (15% to 20% of the total blood volume as measured by the plasma volume and the hematocrit) was removed by venesection. Three to 60 minutes later the same quantity of paredrolinol used in the control test was injected intravenously. The arterial pressure was determined with a mercury manometer by the auscultatory method.

Results. In 5 of the 6 subjects, circulatory collapse occurred either during the venesection or a few minutes after completion of the procedure, as indicated by weakness, marked pallor, sweating, nausea, and a feeling of weight on the epigastrium. The subjects responded slowly, if at all, to commands. One person became unconscious. The blood pressure fell precipitously, and the heart

rate became very slow. In 2 subjects the collapse was not treated, and the patients recovered spontaneously. In 3 subjects paredrolinol was given at the height of the collapse. The results are summarized in Table 1.

TABLE 1.—EFFECT OF THE INJECTION OF PAREDROLINOL ON THE ARTERIAL PRESSURE AND HEART RATE IN NORMAL SUBJECTS BEFORE AND AFTER VENESESECTION.

Subject.	Venesection.	Resting blood pressure (mm. Hg.).	Resting pulse rate (per min.).	Paredrolinol (intravenous).			Maximum blood pressure.	Corresponding pulse rate.	Duration of effect (min.).
				Time after venesection (min.).	Clinical state.	Amount (mg.).			
J. C.	Before	140/90	64	..	Normal	10	185/115	44	20
	After	132/90	74	60	No symptoms	10	162/105	56	10
C.	Before	115/80	80	..	Normal	10	160/100	60	20
	After	106/90	78	55	No symptoms	10	148/100	72	15
K.	Before	102/70	75	..	Normal	10	158/90	54	22
	After	88/62	62	25	Nausea and pallor	10	150/80	50	24
B.	Before	118/74	70	..	Normal	10	170/90	44	20
	After	62/40	40	3	Pallor, nausea unconscious	10	150/90	51	
W.	Before	122/80	66	..	Normal	10	174/100	54	20
	After	50/30	40	8	Nausea, pallor, sweating	10	140/80	60	
F.	Before	118/78	74	..	Normal	15	174/105	60	30
	After	Could not obtain	40	4	Nausea, pallor, sweating	15	130/70	72	

In 3 subjects paredrolinol was injected from 25 to 60 minutes after the venesection, when they were symptom free. Two of the subjects had developed circulatory collapse, but had recovered before the administration of the paredrolinol. In each of these 3 instances there was a rise in arterial pressure and a fall in heart rate. The arterial pressures did not reach as high a level as before venesection. The resting blood pressure, however, was lower after the venesection so that the relative rise was nearly as great after as before venesection. None of the subjects developed any symptoms.

In 3 cases paredrolinol was injected at the height of the collapse. The subjects were pale, sweating, and nauseated, and the hands were cool. In 2 subjects the arterial pressure was 62/40 and 50/30 mm. Hg respectively; in the third it could not be obtained. In each case within 3 minutes after the injection of paredrolinol the systolic pressure had risen to 100 mm. The arterial pressure did not reach the level attained before venesection. The difference between the heights to which the arterial pressure rose before and after venesection was more marked in these subjects than in those who

had received paredrinol from 25 to 60 minutes after venesection. As the blood pressure never returned to the low level present at the height of the collapse, it was difficult to judge the duration of the action of the drug. In the subjects with collapse the heart rate was very slow at the time of the injection. When the arterial pressure was raised by paredrinol, the pulse rate increased, although it remained below the normal resting level.

The 2 subjects who developed collapse but did not receive paredrinol made a much slower recovery. The systolic pressure remained below 100 mm. Hg for 30 minutes, and the subjects complained of weakness, sweating, and nausea for 15 to 30 minutes.

These experiments demonstrate that a decrease in blood volume does not contraindicate the use of paredrinol. When the blood volume is decreased no untoward symptoms occur following the administration of the drug, though the arterial pressure does not rise to as high a level as in normal subjects. In the presence of circulatory collapse caused by such a decrease in blood volume (hemorrhage), paredrinol causes a rise in arterial pressure and shortens the course of the collapse.

These observations indicate that in severe circulatory collapse from acute infectious diseases other factors than a decrease in blood volume are operative in altering the response of the circulation to paredrinol. It may be that in certain instances these changes are secondary to a long-continued reduction in blood volume.

Conclusions. Paredrinol is useful in the treatment of circulatory collapse resulting from hemorrhage, because it causes a rise in arterial pressure and relieves the symptoms of the collapse. The lack of clinical improvement in patients with severe circulatory collapse from acute infectious diseases is due to the fact that the collapse is the result of a combination of factors and not of a simple reduction of blood volume.

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THE CLINICAL IMPORTANCE OF SMALL INTRACUTANEOUS VEINS IN THE HUMAN CHEST.

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IN 1885 Sahli¹⁴ described fine cutaneous phlebectasias whose course paralleled the lower anterior borders of the lungs or the lower margin of the pleura. These visible veins were dendritic in arrange-

ment, corkscrew in appearance, bluish-purple in color, and more pronounced on the right chest wall. Since these vessels were originally observed in patients who suffered from chronic cough, Sahli believed that cough and the resultant alterations of intrathoracic pressure produced congestion and dilatation of the superficial veins. Subsequently Sahli¹⁵ abandoned this explanation, for additional experience indicated that these ectasias were present in normal subjects who had not been afflicted with a chronic cough. Since the veins at the junction of the thorax and abdomen were exposed alternately to positive intra-abdominal and negative intrathoracic pressure during the rhythmic movements of the diaphragm and since inspiratory retraction of the interspace might also cause rhythmic inhibition of the circulation, he concluded that these two physiologic processes could produce adequate intermittent obstruction to blood flow. Although he did not exclude the possibility of provocative developmental anomalies as an additional factor, he believed that the mechanisms mentioned accounted for local venous dilatation in the region of the lower borders of the lungs.

Since Sahli's publications these veins have received consideration only on rare occasions in medical literature. They are not mentioned in the current textbooks on physical diagnosis although their incidence is high in healthy individuals.

Several authors, however, have noted the appearance of similar veins as the result of certain underlying pathologic conditions. Lombardi⁶ described dilatation of the cutaneous veins in the vicinity of the spinous processes of the seventh cervical and first dorsal vertebra. They were present in 90% of tuberculous patients examined by him and constituted "the alarm area of varicosities" and "a new symptom of tuberculosis." Congestion consequent to pleural adhesions at the apex or enlargement of the lymph glands and compression of the deep veins were offered as an explanation for their existence. Fishberg³ observed visible chest veins, occasionally in healthy persons, and frequently in nursing women and in patients with chronic bronchitis, pulmonary emphysema and intrathoracic tumors. Although Vierordt¹⁷ appreciated that these veins appeared in healthy individuals, he regarded them as evidence of collateral circulation. Emphysema, adhesive pericarditis and pleurisy frequently were responsible for their appearance. Neumann⁹ discussed a wreath of minute capillary veins which appeared bilaterally on the anterior chest wall near the attachment of the diaphragm. Elderly individuals with pulmonary emphysema and patients with pleural adhesions in the lower thorax were particularly subject to them. A band of dilated capillaries along the line of diaphragmatic attachment was observed by Hutchinson and Rainy⁴ in patients with right heart failure. Robertson¹¹ reported the development of such veins anteriorly at the level of the lower lung margin and posteriorly at the seventh cervical vertebra. According to him they owed their existence to obstruction of the azygos vein by adhesions

or adenopathy of tuberculous origin. The number of veins was proportional to the severity of the cough, the duration of the disease and the extent of fibrosis but the veins were not necessarily more numerous on the affected side of the chest.

This survey, far from complete, shows the difference of opinion prevailing in regard to the incidence and developmental mechanism of these veins. A systematic study of these peculiar structures in respect to their frequency in health and disease has not been undertaken as far as we can determine.

Observations. In order to investigate these veins 385 patients were examined. While they represented miscellaneous clinical material and, in the main, were unselected, the group intentionally included many instances of pulmonary and cardiac disease in view of the alleged relationship supposed to exist between these conditions and the appearance of veins. A special endeavor was also made to include patients hospitalized for disorders unrelated to the circulatory system, such as duodenal ulcer, diabetes insipidus, enteritis, and so on. Both sexes are represented and the range of ages varied from 14 to 72 years.

The skin was examined for these veins under good light and the location marked with a pencil. Frequently slight stretching of the skin between two fingers facilitated the discovery of small veins, otherwise invisible. Only intracutaneous veins, more or less dendritically arranged, and occurring at the level of the pleural sinuses or around the last cervical and first to fifth dorsal vertebral spines were marked. Often their appearance closely simulates the star-shaped groups of veins in the cortex of the kidney (*stellulae Verheyenii*). No record was made of isolated dendritic veins, occasionally observed in the healthy or other parts of the chest or abdomen, unless they were present in large numbers.

Figure 1 shows a typical example of a ring of veins on the anterior phrenico-costal sinus in a patient with myeloid leukemia. The ring runs from the anterior axillary line on the right to the mid-axillary line on the left without interruption. There was no evidence of pulmonary or cardiac disease.

Figure 2 shows very pronounced and engorged veins along the attachment of the diaphragm in a case of mediastinal tumor. There was a slight compression of the superior vena cava but no compression of the azygos veins at post mortem.

The protocols show that the veins were recorded in 261 (67.7%) of 385 patients examined. Table 1 shows that the incidence of occurrence increases definitely among older subjects. Among 29 patients below the age of 20 veins were present in 14 (48.2%) while they were noted in 46 of 60 people of 60 years or more (76.6%).

TABLE 1.—INCIDENCE ACCORDING TO AGE.

	Age: 14-19.	20-39.	40-60.	Over 60.	Total.
Veins present	14	80	121	46	261
Veins absent	15	63	32	14	124

From Table 2 it becomes evident that these veins were present in only 28 of 54 patients (51.8%) with pulmonary disease (tuberculosis, emphysema, bronchitis). Accordingly no evidence was

TABLE 2.—INCIDENCE IN VARIOUS DISEASES.

Disease:	Pulm. disease.	Cardiac decomp.	Pleural adhesions.	No pulm. or card. dis.
Veins present	28	66	16	95
Veins absent	26	28	19	42

secured to indicate more frequent occurrence in these conditions nor were they more extensive when present. Among 94 decompensated cardiac patients examined (coronary sclerosis, rheumatic



FIG. 1.—Pleural sinus veins in a case of leukemia.

heart disease, syphilitic aortitis, hypertension) the veins were detected in 66 (70.2%) and were absent in 28. In 35 patients visible pleural adhesions were found on fluoroscopic examination. Of these, 10 (20.8%) failed to exhibit superficial chest veins and in 6 the veins were present only on the side opposite to the adhesions; in 5 they were more prominent on the side of the adhesions. In all of these cases adhesions were extensive and in 4 calcification had occurred.

Among 137 patients without demonstrable pulmonary or cardiac disease the veins were detected 95 times (69%). This group consisted of patients with diabetes, peptic ulcer and other diseases.

Table 3 shows the location of the ectatic veins at different areas of the chest. Among 261 positive cases, they were bilateral in the region of the phrenico-costal sinus in 103 (39.5%). In only 5 of these cases were they limited to a circumscribed area; the remainder

showed a longer line parallel to the costo-pleural sinus. The venous ring shown in Figures 1 and 2, running without interruption from right to left of the xiphoid process was noted 42 times in this study. The veins visible posteriorly were seen on or near the midline, in

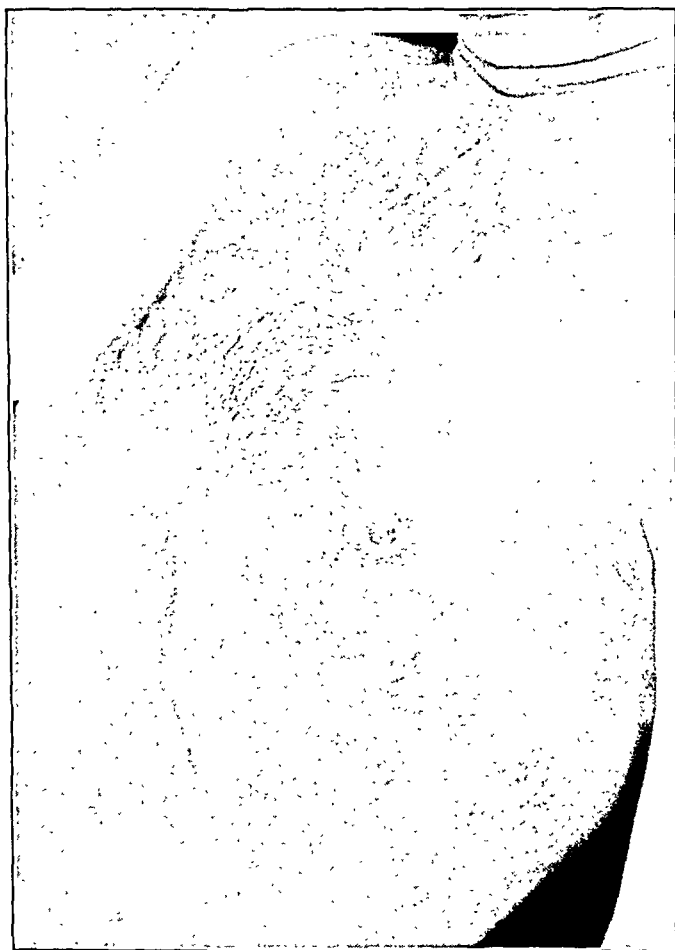


FIG. 2.—Pleural sinus veins in a case with mediastinal tumor

TABLE 3.—LOCATION OF ECTATIC VEINS ON THE CHEST.

Symmetrical	103
Limited to left side	81
Limited to right side	16
Venous ring without anterior interruption	42
At the left anterior costo-mediastinal sinus	8
More pronounced on left side	36
More pronounced on right side	10
On back (seventh cervical-fifth dorsal) in addition	71
Limited to back	13
Limited to xiphoid process	1
Limited to eleventh dorsal spinous process	1
Inner border of Kroenig's isthmus	6

the region of seventh cervical or the first thoracic vertebra; at times they extended down to the third dorsal vertebra and rarely to the fifth. The 8 cases listed as "at the left anterior costo-mediastinal sinus" showed veins from the second or third rib at the left parasternal line and extended downward in an arc following the costo-mediastinal sinus and marking the area of so-called absolute cardiac dullness exactly. When the inner border of Kroenig's isthmus was marked, the veins were evident posteriorly and bilaterally.

These figures indicate that the phlebectasis under discussion follow the borders of the pleural sinus; they are more definitely in evidence at the lower anterior lung margin and most common on the *left* side. When posterior, they occur at the level of the seventh cervical and first to fifth dorsal vertebral spines, rarely near the eleventh dorsal vertebra. In the latter areas they may not be numerous and careful examination may be necessary to disclose their presence. At other times clearly visible red spots a few centimeters in diameter will be noted.

The relation between the veins at the anterior costo-pleural sinus and the attachment of the diaphragm is reflected in Table 4.

TABLE 4.—SITE OF VEINS IN RELATION TO DIAPHRAGM.

Exactly at the attachment of the diaphragm	155
Above attachment but in area of contact	68
Below attachment	6
Above area of contact	12
Elsewhere	5

In 155 of 246 cases displaying veins anteriorly (63%), the fluoroscope revealed that these structures were located exactly at the attachment of the diaphragm. In only 5 cases was there no relation at all to this muscle. Whenever the veins were above or below the contact area, a definite reason for the exception could be found. For example, they were above in patients whose diaphragms were low or horizontal (enteroptosis, pulmonary emphysema) and below when the skin had been stretched by large pendulous breasts or a recent marked reduction of weight had occurred. It was common to find the veins on one side at the attachment of the diaphragm and on the other side in the contact area. In some cases they began at the attachment and ascended posteriorly to the contact area. These are included in the first group in Table 4.

In 17 patients the veins were studied by means of the capillary microscope in order to determine the direction and rate of blood flow in relation to the respiratory cycle. In all of this group the veins were quite prominent and the blood stream was readily visualized when filters were employed. In 14 of this group no change of blood flow occurred with respiration; the ordinary irregular change from stagnation and flow observed in capillary studies was found and regarded as normal. A slight slowing during inspiration was visible in 3 patients but was attributed to the expansion

of the chest and consequent slight compression of the veins by the lens. Marked slowing and even standstill of blood flow occurred during the Valsalva experiment and is readily explained by the marked increase of venous pressure typical of this test.

In 11 patients biopsies were made of the veins. The skin veins were found to be of unusual size for their location. The sections failed to reveal anything unusual in other respects. They are lined by a single layer of endothelium and are located in the corium.

Discussion. These cutaneous veins were present in a majority of the cases examined. Their number and incidence increased with age. No definite correlation between their number or incidence and various pathologic chest diseases (cardiac decompensation, pulmonary tuberculosis, adhesive pleuritis, and so on) could be discovered. This rule holds for the veins of Sahli as well as for those described by Lombardi. Only in cases with extensive, calcified pleural adhesions and in 2 cases of mediastinal tumor were the veins definitely more pronounced on the side of the lesion or bilaterally.

The veins are located near or at the borders of the pleural sinuses. They are most common on the left side over the anterior phrenico-costal sinus. From the locations of the veins, enumerated above, it will be seen that their appearance is not dependent upon diaphragmatic movements but they are related to the borders of the pleural sinuses. Despite their position, they might be called "pleural sinus veins" since they are located at the anterior phrenico-costal sinus, the left anterior costo-mediastinal sinus, and at the upper and lower ends of the posterior mediastinal sinus. Study of blood flow in the dilated veins failed to reveal any relation of rate or direction of flow with phases of the respiratory cycle.

A congenital anomaly is not responsible since the incidence of occurrence increases with age and the veins do not follow the thoracic segments but the location of the pleural sinuses. Apart from 2 patients with mediastinal tumor there was no congestion of the larger veins, so that a very *localized* disturbance would seem to be responsible.

The last two or three intercostal veins do not have a double communication both to the azygos (or hemiazygos) and the internal mammary veins and they differ somewhat anatomically from the upper intercostal veins. This does not however adequately explain the appearance of the sinus veins since they are also found along the left anterior mediastinal sinus in an uninterrupted line.

Since no pathologic lesion in the chest need be present and a congenital anomaly would appear to be eliminated and since the appearance of the veins is not dependent on diaphragmatic movements, and the incidence increases as older age groups are examined, another possible explanation deserves consideration.

Any sudden physical exertion such as running up a flight of stairs, cough, pressure during defecation, even bending, causes

increased intrathoracic pressure, as in a Valsalva experiment. A marked increase of intrathoracic pressure prevents blood from flowing into the thoracic veins and causes a marked elevation of venous pressure. Values exceeding 500 mm. H₂O have been obtained in a Valsalva experiment.¹ The transmission of this increase of pressure may be prevented in some areas by venous valves; but if the valves are incompetent or the veins in some areas lack them, increased pressure may cause congestion in the tributaries. The fact that these veins are more or less limited to the borders of the pleural sinuses and not located all over the chest may be due to a special arrangement of the veins and their communication with the superficial vessels at these locations, not as yet understood nor investigated.

It seems rather probable that intrapulmonic pressure is especially high at the sites of the pleural sinuses during the Valsalva experiment. The available knowledge concerning intrathoracic pressures at different areas under normal and abnormal conditions is very meager. Some physiologists and clinicians deny *a priori* the possibility of an unequal distribution of intrathoracic-pleural pressure. While exact measurements are more important than theoretical considerations, at present varying opinions exist on the basis of such investigations. According to some students the pressure in the potential intrapleural space is the same at different areas,^{2,12,18} while others have found definite, even marked differences^{5,7,8,10,13} or assume that such differences may exist.^{15,16} The fact that bullæ in advanced emphysema usually occur at the apices, the anterior margin of the lung, and at the bases, that is, at the same sites at which the "pleural sinus veins" appear, may be the result of a special elevation of pressure in these areas during cough, pressure and so on.

A knowledge of the existence of these structures, their high incidence, and the exact location may have some importance since they readily indicate the site of the pleural sinuses; this may aid in the differential diagnosis of some intrathoracic diseases.

Conclusions. Ectasia of small intracutaneous veins located in the neighborhood of the pleural sinuses is described. An examination of 385 patients revealed that the appearance of these veins is not the result of pulmonary, pleural or cardiac disease. They are found in healthy people. Their incidence increases with age. An explanation of their developmental mechanism is offered.

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LEUKOPENIA IN NEGRO WORKMEN.

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DURING the summer of 1939 we were studying the physiology of Negro sharecroppers in Mississippi and in the course of examining their blood noticed that the majority of them had a leukopenia. Native Whites living under approximately the same conditions of work and diet had normal counts. One of us, upon whom counts were made both in Boston and Mississippi, remained within the usual range, and one of the leukopenic workmen brought to Boston has continued to have white counts as low as he had in Mississippi. The leukopenia is possibly a local racial characteristic and seems worthy of record.

The climate in this region was hot and moist with the temperature during the middle of the day almost always over 90° F. and the humidity over 60%. The subjects were young and apparently healthy manual laborers working in the cotton fields. During most of the period from June 15 to August 19, when these counts were made, their work was irregular, for the crops were being "laid by." Medical examinations were made and histories taken by Drs. Thompson and Gedgoud, the details of which they are presenting elsewhere;⁵ the part of their study which is relevant here may be summarized briefly as follows: None of the subjects was observed to have any active disease at the time of the examination; 75% of them had had malaria ("chills") in childhood but not within 2 years; 50% had had gonorrhea and 10% (*i. e.*, 2 individuals) were finishing courses of treatment for syphilis acquired 1 or 2 years before. They had, for the most part, been treated for these latter diseases by competent physicians but they had not all returned for the full course of treatment. They had no hookworm. Only one showed clear-cut sickling; 2 others showed an occasional crescent-shaped cell after the slide had stood for 6 hours. With one exception (a man who showed slight symptoms of pellagra), there was no evidence that their diet was inadequate. It was difficult to get

an accurate picture of their eating habits, but it was clear that most of them had milk, eggs, meat, and a variety of vegetables and roots during a considerable part of the year, though occasionally they might be reduced to corn, beans, potatoes, and salt pork.

We were unable to find any clear relation in these subjects between their leukopenia and the diseases which they had had, but the average white count for the few who said they had not had malaria was a little higher than for the many who had had it.

The counts were made upon finger blood taken in the morning from fasting subjects who had been lying down for half an hour or more. Some of the counts, especially the low ones, were repeated—that is, another finger was pricked if the first count was found to be unusually low. A few counts were made in the afternoon on some of the same subjects when they were neither fasting nor resting, and these averaged 6500, which is 3200 higher than the morning values.⁴

Table 1 gives the data for the red cells as well as for the white cells for the subjects who were most extensively studied, and also the average figures for all the Negroes, which includes 30 additional subjects, mostly boys from 8 to 16 years of age, on whom a single count was made.

The red cells of both Negroes and Whites were normal, on the average, in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. A few of the Negroes had blood pictures suggestive of a mild normochromic macrocytic anemia, but these cases were not striking. The total red cell count was on the average a little lower than the usual normal figure of the textbooks.⁶ In general, it appeared as if their red cell level was about that of a normal White female, and their total hemoglobin correspondingly a little low. This may be a racial difference as it has been reported that Negro infants in Michigan have less hemoglobin than white infants.³

The white cell counts were abnormally low. The 2 subjects in the adult Negro group marked with asterisks were the only ones who appeared to have white blood, and it is striking that both of them had counts of over 7000, while all the others were below 6200 and the majority were below 4000. Our values were much lower than those obtained by Bryan, Chastain, and Garrey¹ on a similar number of healthy Whites of about the same age and living in nearly the same region. Our own values upon Whites native to Mississippi were few but lie within the usual range (Table 1).

There was no easy explanation to hand for this leukopenia in the Negroes. Their red counts and oxygen capacities were slightly lower than the average normal (Table 1), and this gave rise to the idea that perhaps there was a slight iron deficiency, though the normal values for the hemoglobin per cell and the normal white counts on the White sharecroppers who ate nearly the same food, gave no support to this hypothesis.

TABLE 1.—MORPHOLOGIC CHARACTERISTICS OF BLOOD OF NEGRO AND WHITE SHARECROPPERS.

Subject.	Date, 1939.	Cell volume, %.	Oxygen capacity, vol. %.	Hemoglobin, gm. %.	Red cells, millions/mm. ³	Mean corpuscular volume, cubic micra.	Mean corpuscular Hb., micromicrograms.	Mean corpuscular Hb. concentration, %.	Leukocytes, number/mm. ³	Differential count.					
										Polymorphs, %.	Lymphocytes, %.	Monocytes, %.	Eosinophils, %.	Basophils, %.	
<i>Negroes.</i>															
B.C.	6/17	43.2	18.27	13.6	4.79	90	28	31	4000	
J.C.	6/19	40.8	4.80	85	4200	60	23	7.5	8.5	1	
A.P.	6/20	41.2	18.10	13.5	4.34	95	31	33	2800	67	27	6	0	0	
W.B.	6/21	43.8	18.18	13.5	4.40	100	31	31	2250	55	37	5	2	1	
J.B.	6/22	44.2	19.18	14.3	4.92	90	29	32	3000	53	39	3	4	1	
C.A.	6/23	42.0	18.16	13.5	4.69	90	29	32	3650	51	36.5	6	4	2.5	
J.J.	6/24	42.2	18.40	13.7	4.86	87	28	32	4500	54	26	11	5.5	3.5	
A.B.	6/26	43.5	18.76	14.0	4.96	88	28	32	2950	58	29	9	3	1	
J.A.	6/27	40.1	18.02	13.4	4.25	94	32	33	2300	37.5	36.5	9	12	3	
W.A.	6/28	44.9	4.27	105	3480	38	52	5	5	0	
A.G.	6/29	39.7	16.67	12.4	3.20	124	39	31	2400	34	62	2	1	1	
C.J.A.	6/30	43.8	18.90	14.1	4.56	96	31	32	3250	
J.S.	7/3	42.6	16.76	12.5	4.93	87	25	29	3600	57	36	2	2	3	
J.B. II*	7/1	45.0	19.55	14.6	4.56	99	32	33	7200	44.5	51	2.5	1.5	0	
A.E.	7/4	43.6	18.45	13.7	4.20	104	33	31	6100	56.5	37.5	4	0	2	
T.H.	7/5	46.4	18.58	13.8	5.17	90	27	30	3450	22	58	10	5	5	
M.M.	7/6	45.0	19.47	14.5	5.36	84	27	32	5100	49	43	8	0	0	
M.B.	7/7	43.7	18.32	13.6	4.58	95	30	31	3750	56.5	34	6.5	3	0	
R.B.	7/10	40.8	17.19	12.8	4.89	83	26	31	4750	52.5	39	1	6.5	1	
C.F.	7/11	43.8	18.87	14.1	3.74	117	38	32	3800	44	51	4	1	0	
R.P.	7/12	41.4	17.74	13.2	3.78	110	35	32	3650	41	49.5	2.5	4.5	1.5	
E.J.H.	7/13	40.2	17.20	12.8	4.14	97	31	32	5000	50.5	43	4	2	0.5	
C.W.*	7/14	41.2	19.43	14.5	5.26	78	28	35	8050	71	21	5.5	1.5	1	
Average	...	42.7	18.31	13.6	4.55	95	30	32	4050	50	39.7	5.5	3.5	1.3	
Average for all negro subjects studied (total of 51)					4.36	4830	50	38	6	5	1	
<i>Whites.</i>															
Pent.	7/27	46.1	20.71	15.4	4.35	106	35	33	8300	78.5	16	3.5	2	0	
T.G.	7/29	43.1	18.81	14.0	4.41	99	32	32	8550	58.5	19.5	5	16.5	0	
A.F.	7/31	47.0	20.62	15.3	4.72	99	32	32	8990	52.5	35.5	6.5	4.5	1	
J.B.	8/1	40.8	18.55	13.8	4.35	94	32	34	6450	53	27	7.5	11.5	1	
F.W.	8/2	42.7	19.61	14.6	4.55	94	32	34	6150	54	36	4	4.5	1	
D.W.	8/2	45.6	20.43	15.2	4.61	99	33	33	5900	55	35	6	3.5	0.5	
J.T.S.	8/4	47.5	20.14	15.0	4.50	105	33	31	8850	70	23	7	0	0	
Average	..	44.8	19.83	14.8	4.50	99	33	33	7600	60	27.5	6	6	0.5	

Method. To test this we selected 18 healthy Negroes whose white counts ranged from 2300 to 4200 and divided them into 3 groups, each of which contained 2 subjects with slight, 2 with moderate, and 2 with marked leukopenia. The averages for the groups were 3440, 3290 and 3270. The first group was given no medication. The second got four 3-grain tablets of ferrous sulphate (Feosol) per day, two in the morning and two in the

evening. The third got 1 oz. daily of "Valentine's Liver Extract with Iron"* (5 grains added available iron per oz.), $\frac{1}{2}$ oz. in the morning and $\frac{1}{2}$ oz. in the evening. This may be considered as equivalent to giving aqueous liver extract, 1 oz., and metallic iron, 5 grains, daily, which is approximately the same amount of metallic iron as is contained in the daily dose of ferrous sulphate. The iron was given for 16 days, the liver for 12. The last determinations on the group taking liver were made 3 days after taking the last dose. The conditions of the experiment made it impossible to be sure that all doses were taken, but the great majority were. White and red blood cell counts were made at intervals for 16 days after the iron and liver had been started.

It was not feasible ordinarily to get all the subjects to come in on the same day, so the counts are arranged in 3 groups: those taken between the 5th and 9th days inclusive, those taken between the 10th and 13th inclusive, and those taken on the 16th day after beginning the treatment.

TABLE 2.—EFFECTS OF IRON AND OF LIVER AND IRON ON THE WHITE BLOOD CELL COUNT OF NEGRO SHARECROPPERS.

Subject.	Before start of experiment.	5-9th day after start of experiment.	10-13th day after start of experiment.	16th day after start of experiment.
<i>Controls.</i>				
W.B.	2475
J.B.	3100	..	4550	4000
C.F.	3800	..	5000	3900
M.B.	4050	3900	..	3200
R.P.	3600	..	4400	4200
J.S.	3600
Average	3440	3900	4650	3825
Av. change of those counted	..	-150	+1150	+190
% change of those counted	..	-4%	+33%	+5%
<i>Iron</i>				
J.C.	4200	7900	..	6900
A.P.	3250	5000	..	5600
C.A.	2950	5400
A.G.	2400	5600	5200	5800
C.J.A.	3250	4250	3200	3200
M.B.	3750	4075	5900	5300
Average	3300	5370	4767	5360
Av. change of those counted	..	+2070	+1640	+1990
% change of those counted	..	+63%	+53%	+60%
<i>Liver and Iron</i>				
B.C.	4000	3900	4200	3800
A.B.	2900	..	5400	4300
J.A.	2300	3500	3300	2700
T.H.	3400	5500	5300	5500
W.A.	3450	5500	5800	5100
W.S.	3550	5000	5700	6000
Average	3290	4680	4950	4570
Av. change of those counted	..	+1340	+1660	+1280
% change of those counted	..	+39%	+50%	+39%

The results are given in Table 2. This shows that before the 9th day there was an increase of 2080 on the average, or just over 60%,

* Very kindly supplied by the Valentine Company, Inc., Richmond, Va.

in the white count in the group that got iron. Those who got liver extract with iron increased 1360 (40%) in the same period. Seven to 11 days later the figures were substantially unchanged.

Four things stand out in the table: the prompt and definite response in 10 out of 12 subjects; the rather low final values; the fact that 1 man in each group of 6 did not respond at all; and that liver and iron was apparently less effective than iron alone. With respect to the speed of the response, the data suggest that the response did not reach its maximum until after the 5th day. There was, however, no general rise after the 9th day.

TABLE 3.—ABSOLUTE NUMBERS OF WHITE CELLS PER CUBIC MILLIMETER IN 18 NEGRO SHARECROPPERS.

	Neutrophils, number/ mm. ³	Lymphocytes, number/ mm. ³	Monocytes, number/ mm. ³	Eosinophils, number/ mm. ³	Basophils, number/ mm. ³
<i>Before Experimental Period of Taking Iron or Liver and Iron.</i>					
Highest	2520	1970	360	336	170
Lowest	750	900	48	0	0
Mean of 18 subjects .	1546	1300	203	124	41
<i>After Experimental Period of 12 to 16 Days of Taking Iron or Liver and Iron.</i>					
Highest	4620	2700	550	720	225
Lowest	1350	675	152	106	0
Mean of 12 subjects .	2700	1810	298	251	38

There are two general points of view which can be taken concerning the data. One is that these low blood counts are normal for the Negroes and that the effect of the iron (for it does not appear that the liver had much effect) was to: *a*, artificially stimulate the bone marrow to a general hyperactivity; or, *b*, perhaps irritate the intestine and so cause a leukocytosis. The other point of view is that leukopenia is abnormal for Negroes and that the iron (or conceivably a trace of something else in the preparations) made up for a deficiency in the diet. This latter view implies that iron is helpful in the production of leukocytes. There is some evidence for this in the literature on iron deficiency anemia, for in so-called "idiopathic" hypochromic anemia, in which there is frequently an initial leukopenia, the number of white cells increases after the administration of iron. On the other hand, one of the Negroes brought to Boston upon whom counts have been made repeatedly still gives the same rather low values (4000±) in spite of the change of diet (with the incorporation of yeast, raisins, tomato juice, and milk), of climate, and a considerable gain in weight. He had one of the higher counts in Mississippi and had been unaffected by the liver extract.

On returning to Boston we tried giving ferrous sulphate to 2 White subjects, 1 of whom habitually has low white counts. The same procedure was followed as with the Negroes, but unlike the Negroes these subjects showed no change in the number of leukocytes. We also tried 1 subject with liver extract but produced no change in the count.

The differential counts show that the leukopenia is not confined to one type of cell, though in several individuals the neutrophils were diminished much more than the lymphocytes.² The increases observed after taking iron or liver and iron were in all types, but in most subjects the neutrophils showed the greatest increase. The absolute number of neutrophils in most of the 18 subjects chosen for the study of the effects of iron and liver was very low (Table 3). The monocytes also were below normal, while the lymphocytes, eosinophils, and basophils were within the normal range, though the lymphocytes were at the lower border of normal. After the iron all types except the basophils were increased, the eosinophils and neutrophils showing the greatest changes. The iron had no significant effect upon the red cell count.

Summary. 1. Healthy Negro sharecroppers in Mississippi examined in the summer of 1939 showed in a majority of instances a leukopenia and a slightly lower erythrocyte level and oxygen capacity than normal Whites.

2. This leukopenia was principally a neutropenia, but involved the lymphocytes as well in some cases.

3. Administration of iron caused a marked increase in the leukocyte count of 10 out of 12 selected sharecroppers, the increase being largely in the neutrophils.

4. White sharecroppers in the same region eating about the same diet as Negroes showed no leukopenia.

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MURAL THROMBI IN THE HEART AS A SOURCE OF EMBOLI.

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THOUGH mural thrombi are a common source of emboli, exact figures pertaining to this relationship are difficult to obtain since it is often impossible to differentiate between embolic and thrombotic arterial occlusion. Thus McKechnie and Allen³ have written that "the terms 'embolism' and 'thrombosis' when applied to our material indicate the apparent diagnosis. No methods exist for

differentiating these two conditions with absolute certainty." deTakats² states that "It has been my experience with . . . arterial thrombosis and arterial embolism, that the differential diagnosis between these two types of arterial occlusion is often clear cut, sometimes difficult and occasionally impossible." He asserts, however, that "the differential diagnosis between arterial thrombosis and embolism has much more than academic interest." Blumer¹ has stated that "it cannot be assumed that clinical phenomena resulting from arterial occlusion . . . are all embolic in origin. Some of them are doubtless due . . . to thrombosis Owing to the difficulty of deciding, even on the autopsy table, whether a given lesion is thrombotic or embolic, exact figures as to the relative frequency of the two lesions are impossible to obtain."

Accordingly, in order to determine the relative importance of mural thrombi as a source of emboli, an indirect approach to the problem has been attempted. If mural thrombi are an important source of emboli, then patients having mural thrombi should have a significantly higher incidence of infarction of the various viscera than a control group.

The clinical and pathologic records of 771 consecutive adult autopsied patients who died of heart disease were examined as to the occurrence of mural thrombi and infarction. These cases occurred in 6,285 consecutive postmortem examinations done at the Cleveland City Hospital from January, 1930, to June, 1939.

One or more mural thrombi in the right side of the heart were found in 161 cases and of these, 93 (57.8%) showed one or more pulmonary infarcts. The remaining 610 cases which had no mural thrombi in the right side of the heart included 128 instances of pulmonary infarction, an incidence of 21%. This difference is highly significant* statistically. It indicates that in autopsied patients pulmonary infarction is almost 3 times as frequent as the presence of mural thrombi in the right side of the heart as in their absence.

One or more mural thrombi were present in the left side of the heart in 193 cases, and of these, 94 (48.7%)† showed one or more infarcts in the brain, kidneys, spleen, intestines and/or extremities. In contrast to this, 578 cases without mural thrombi in the left side of the heart included 135† instances of infarction involving one or more of the viscera just listed, an incidence of 23.4%. Again the difference is highly significant statistically and it can be concluded that in autopsied patients infarction of the brain, kidneys, spleen,

* In this article, the term "significant" refers to a difference which could be produced by chance in less than 5% of trials as demonstrated by application of the chi square test; "highly significant" refers to a difference so great that it could be produced by chance in less than 1% of trials, again as demonstrated by application of the chi square test.

† The figure is actually lower than the true value since the brain was examined in only 56% of the cases.

intestines and/or extremities is over twice as common in the presence of mural thrombi in the left side of the heart as in their absence.

The results in respect to the four types of heart disease which occurred frequently enough to permit statistical analysis are summarized in Tables 1 and 2. In hypertensive heart disease and in coronary artery disease with or without myocardial infarction the incidence of pulmonary infarction in the presence of mural thrombi in the right side of the heart was 3 to 4 times as great as in their absence (Table 1), a highly significant difference. In rheumatic heart disease, the incidence of pulmonary infarction was over twice as great in the cases with mural thrombi in the right side of the heart (Table 1), a significant difference.

TABLE 1.—THE RELATIONSHIP OF THE PRESENCE OR ABSENCE OF MURAL THROMBI IN THE RIGHT SIDE OF THE HEART TO PULMONARY INFARCTION.

Type of heart disease.	Cases with mural thrombi in right side of heart.			Cases without mural thrombi in right side of heart.		
	No. cases.	No. with pulmonary infarcts.	% with pulmonary infarcts.	No. cases.	No. with pulmonary infarcts.	% with pulmonary infarcts.
Hypertensive heart disease (147 cases)	34	22	64.7	113	23	20.4
Coronary artery disease without myocardial infarction* (94 cases)	19	14	73.7	75	15	20.0
Coronary artery disease with myocardial infarction* (133 cases)	42	27	64.3	91	18	19.8
Rheumatic heart disease (116 cases)	23	13	56.5	93	25	26.9

* Whether there was associated hypertensive heart disease or not made no appreciable difference.

TABLE 2.—THE RELATIONSHIP OF THE PRESENCE OR ABSENCE OF MURAL THROMBI IN THE LEFT SIDE OF THE HEART TO INFARCTION IN THE BRAIN, KIDNEYS, SPLEEN, INTESTINES AND/OR EXTREMITIES.

Type of heart disease.	Cases with mural thrombi in left side of heart.			Cases without mural thrombi in left side of heart.		
	No. cases.	No. with infarcts in brain, etc.	Per cent with infarcts in brain, etc.	No. cases.	No. with infarcts in brain, etc.	Per cent with infarcts in brain, etc.
Hypertensive heart disease (147 cases)	31	13	41.9	116	20	17.2
Coronary artery disease without myocardial infarction* (94 cases)	29	16	55.2	65	21	32.3
Coronary artery disease with myocardial infarction* (133 cases)	81	41	50.6	52	15	28.8
Rheumatic heart disease (116 cases)	22	11	50.0	94	22	23.4

* Whether there was associated hypertensive heart disease or not made no appreciable difference.

Infarcts in the brain, kidneys, spleen, intestines and/or extremities occurred 2.4 times more often in hypertensive heart disease when mural thrombi were present in the left side of the heart as when they were absent (Table 2), a highly significant difference. In coronary artery disease with myocardial infarction and in rheumatic heart disease, infarcts involving the brain, kidneys, spleen, intestines and/or extremities were about twice as frequent when mural thrombi existed in the left side of the heart (Table 2), a sig-

nificant difference. In coronary artery disease without myocardial infarction, infarcts in the brain, kidneys, spleen, intestines and/or extremities were 1.7 times as frequent when mural thrombi were present in the left side of the heart as in their absence (Table 2), but this difference was not statistically significant. This may be due to the fact that the total number of cases in this group was not large and/or due to the fact that these cases had considerable peripheral vascular disease with its attendant possibility of infarction by thrombosis *in situ*.

Summary. In 771 consecutive adult autopsied patients who died of heart disease, pulmonary infarction was almost 3 times as frequent in those cases with mural thrombi in the right side of the heart as in those cases without. Infarcts of the brain, kidneys, spleen, intestines and/or extremities were more than twice as common in cases with mural thrombi in the left side of the heart as in their absence. A similar relationship was found to exist in regard to hypertensive heart disease, coronary artery disease with or without myocardial infarction, and rheumatic heart disease, with one exception. In coronary artery disease without myocardial infarction, infarcts in the brain, kidneys, spleen, intestines and/or extremities were 1.7 as frequent when mural thrombi were present in the left side of the heart as in their absence but the difference was not statistically significant. This exception may be due to the small size of the series and/or to the fact that these cases showed considerable peripheral vascular disease which no doubt increased the incidence of infarction due to thrombosis *in situ*. These observations indicate that mural thrombi in the heart are a significant cause of embolic occlusion of arteries in both the lesser and greater circulations.

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APOPLEXY APPARENTLY PRECIPITATED BY LOW BLOOD PRESSURE.

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THERE have been reported⁴ transient episodes of hemiplegia and aphasia in elderly arteriosclerotic patients, attributed to acute hypotension, but it is rarely possible to prove the relationship be-

cause there is not likely to be a record of the blood pressure just prior to such a crisis. For example, Behrend and Riggs^{1a} reported a series of cerebral complications following surgical operations in each case of which the brain showed widespread degenerative changes attributed to the effects of acute anoxia. They consider the anoxia was produced, at least in part, by an alteration in blood pressure occurring as a result of the effect of surgical operation and of the anesthetic on a patient with impaired cardiocirculatory efficiency, but they did not publish data concerning blood pressure before the actual onset of the ictus. An exceptional report is that of Wolf and Siris who published a report of 4 cases of operation upon the nervous system complicated by the development of multiple cortical hemorrhagic necroses. In each case the blood pressure was being carefully recorded, and acute hypotension seemed to have been the precipitating factor. Although they stated that there was no occlusion of the vessels supplying or draining the involved areas of brain, they did record in one instance the thrombosis of a small cortical vein, which seemed to be secondary to the cortical degeneration.

We present here 3 fatal cases in which the blood pressure was being recorded hourly following operation, and in which cerebral vascular accidents occurred at a low point of a gradual drop in blood pressure. Such tragic postoperative complications are less common than transitory or non-fatal apoplectic insults, but the mechanism involved may be similar. Furthermore, the study of these cases may shed light on the pathogenesis of the common cerebral vascular accidents, unassociated with operation, the onset of which is usually not associated with great exertion or even mental excitement.⁵

Case Reports. CASE 1.—A 61-year-old white male, whose blood pressure was 135/75, had an abdominal exploration and biopsy from the liver for inoperable carcinoma of the stomach. The patient's postoperative course was good for the first 24 hours. His blood pressure stayed at 120/65 and he moved all his extremities. On the day following the operation the blood pressure gradually dropped to 85/50 and at one time was 76/30, at which time left hemiplegia set in. The patient was given intravenous infusions and the blood pressure promptly rose. However, there was deepening stupor until death 3 days postoperatively.

Autopsy revealed evidence of recent operation and the carcinoma of the stomach. There was also bronchopneumonia and infarction of the left lower lobe of the lung and of the right kidney. There was moderate arteriosclerosis of the aorta and coronary arteries. The basilar artery was markedly sclerosed but the other arteries associated with the circle of Willis were only slightly sclerosed. There was beginning infarction of the right frontoparietotemporal region of the right cerebral hemisphere. The infarction included primarily the cortex and penetrated the white matter for only about 1 cm. In many areas of the softened cortex there were pinpoint hemorrhages. Although there was no thrombus in the right middle cerebral artery itself, one of its superficial branches and several other pial vessels

lying over the infarcted area contained whitish spiral thrombi. The area of cerebral softening was much greater than seemed to be accounted for by the thrombosis of these small vessels, which may have been secondary. Microscopic study of the brain revealed senile plaques and multiple early infarcts. The white thrombi in the pial vessels consisted of a meshwork of fibrin and masses of platelets in which erythrocytes were caught.

CASE 2.—The patient was an 88-year-old white male, who underwent a transurethral prostatic resection (2 gm. of tissue removed) for contracted bladder neck, under spinal anesthesia. The biopsy revealed adenofibromatous hyperplasia.

Following the operation the patient was nervous and tense but fell into a natural sleep. Twenty-eight hours after the operation, in response to questions, he would only turn his head. This unresponsiveness corresponded with a gradual fall in blood pressure to 95/55. At this time examination revealed a slight stiffness of the neck, marked drowsiness and the presence of Babinski's sign on the right side. Three days later the patient was clearly suffering from a right hemiplegia and had an intermittent fever with evidence of urinary infection. He died 12 days after his operation.

Autopsy revealed multiple pulmonary emboli arising from the right iliac vein, bronchopneumonia, multiple infarcts of the kidneys, and infarction of the left frontoparietal and both occipital portions of the cerebrum.

Examination of the brain revealed moderate atrophy of the convolutions, minimal sclerosis of the cerebral vessels and no evidence of thrombosis of the vessels at the base of the brain. There was a soft red area, 4 by 6 cm., on the surface of the right basofrontal region, which extended back into the Sylvian fissure to the island of Reil. There was a similar area, 4 by 5 cm., on the left occipital lobe and another, 2 by 3 cm., over the right occipital pole. Coronal sections of the brain showed the cortex in these three regions to be hemorrhagic with yellowish spots indicative of infarction. There was very little involvement of the white matter of the brain. Microscopic studies of the defective areas of the brain revealed multiple infarcts both old and recent. Some of the recent infarcts had small hemorrhagic areas. One small vessel in the right occipital region was thrombosed.

CASE 3.—This patient was a 77-year-old white male whose blood pressure had been 146/78 two years ago and at present admittance was 164/82. Under spinal anesthesia a transurethral prostatic resection was performed for benign prostatic enlargement. At the end of the operation the patient knew his name but was disoriented for place, time and his own age. At this time his blood pressure was 158/95, but in the next 4 hours it proceeded to drop gradually to 80/40, at which time there was stertorous breathing. The patient was given intravenous gum acacia, saline solution and blood transfusion with a subsequent rise in blood pressure to 130/70. That night there was weakness of the right side of the face and the next morning there was a right hemiplegia, complete except for the toes. There was increased knee jerk and positive Babinski sign on the right. The blood pressure and temperature gradually rose and the patient died 5 days after operation.

Autopsy revealed marked arteriosclerosis of the aorta and moderate sclerosis of the coronary arteries. There was marked cerebral edema with flattening of the convolutions and notching of the uncinate gyri by the tentorium. The vessels of the circle of Willis were moderately sclerosed but not occluded. There were multiple infarcts 1 to 2 cm. in diameter, involving primarily the cortex of the occipitoparietal region of the left cerebral hemisphere. Some of these regions were hemorrhagic. There were other infarcts scattered through the right lateral lobe of the cerebellum and one small one in the left dentate nucleus. Microscopic studies of the affected areas reveal white thrombi in the pial vessels overlying infarcts both in the cerebrum and the cerebellum.

Discussion. It is stated that low systemic blood pressure with subsequent stasis and anoxemia causes not only cerebral degeneration but also damage to the vessel walls.³ From the evidence furnished by our cases, it is impossible to tell whether the cerebral necrosis and the thrombi in the overlying pial vessels are causally related to each other. Since the occluded vessels were so small and few in relation to the widespread extent of the cortical necrosis, it might be thought that the thromboses were secondary. Such problems are very complicated and must include consideration of the degree of arteriosclerosis, the degree and duration of arterial hypotension, the length of time from the stroke to the death of the patient and the care with which thrombi are sought microscopically. Behrend and Riggs^{1b} have emphasized that a multitude of conditions may be predisposing factors in the production of lesions due to cerebral anoxia. They have mentioned particularly organic heart disease, anemia, anatomic factors, age, metabolic disorders, surgical emergencies, anesthesia and nutritional deficiencies. It is not unlikely that the degenerative changes reported by Behrend and Riggs^{1a} and others, the hemorrhagic necroses without thrombosis reported by Wolf and Siris,⁶ and the hemorrhagic necroses with white thrombosis of pial vessels of the present series are all sequels of cerebral anoxia. Whether the more common cases of "cerebrovascular accidents" in the aged are to be explained on this basis remains to be learned. At least, one should be wary of accepting a red friable clot in a large offshoot of the circle of Willis as the "obvious" cause of an infarct in the region normally supplied by the vessel. It is possible that such a clot is secondary to a sequence of events including stasis, degenerative changes in the cortex and thrombosis of small blood vessels.

Our cases are of significance primarily because they demonstrate the clinical onset of so-called apoplectic strokes in elderly men, coincident with a *drop* in blood pressure. It may prove to be worth while in such cases with progressive drop in blood pressure to treat not only the threatened state of shock by temporarily lowering the head and other usual methods but also the possible beginning thrombosis by administration of anticoagulants such as heparin. In addition, Cobb has recommended the use of cerebral vasodilator drugs, the best being carbon dioxide.²

Summary. In each of the 3 cases reported there was a slow post-operative drop in systemic arterial blood pressure in an elderly arteriosclerotic male. When the pressure reached a low level, there occurred an "apoplectic stroke" marked by unconsciousness and progressive hemiplegia. Death ensued 1, 10 and 5 days, respectively, after the stroke. Necropsy revealed widespread areas of partly hemorrhagic necrosis in the cerebral cortex with little involvement of the subjacent white matter. There were thrombi in neither

the main arterial nor venous trunks, but some of the pial vessels lying over the center of the necrotic areas of the cortex were occluded with thrombi consisting largely of fibrin and masses of platelets.

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BOOK REVIEWS AND NOTICES

SHOCK. BLOOD STUDIES AS A GUIDE TO THERAPY. By JOHN SCUDDER, M.D., Med. Sc.D., F.A.C.S. From the Surgical Pathology Laboratory of the College of Physicians and Surgeons, Columbia University, and the Department of Surgery, the Presbyterian Hospital, New York City. Pp. 315; 58 illustrations, 5 plates (3 in color). Philadelphia: J. B. Lippincott Company, 1940. Price, \$5.50.

THE author of this book spends a great deal of time and energy saying just how bad potassium really is only to conclude: "To state that shock is due to potassium poisoning alone is fallacious. That alterations in potassium in both the blood and body fluids serve as a measure of profound cellular changes is probably more correct." With this conclusion most of the workers in this field would agree, but as a sports writer would put it—"It seems a long run for a short slide."

The emphasis on hemoconcentration in shock is good, as is the wealth of historical material made available through the bibliography. The book is attractively printed. N. F.

ESSENTIALS OF THE DIAGNOSTIC EXAMINATION. By JOHN B. YOUMANS, B.A., M.S., M.D., Associate Professor of Medicine and Director of Post-graduate Instruction, Vanderbilt University Medical School. Pp. 417; 36 illustrations (6 in color). New York: The Commonwealth Fund, 1940. Price, \$3.00.

THIS pocket-sized handbook is intended to serve the practitioner of internal medicine as a guide in the essentials of sound diagnostic procedure. Chapter one, numbering only 14 pages, gives the barest essentials on the subject of history taking. Yet brief as it is, it offers excellent advice on routine, manner and method that will safeguard the physician against gross errors of omission. Much more detailed (142 pages) is the excellent chapter on the physical examination, giving an adequate and orderly review of the eliciting and interpretation of a wide range of physical signs. The outstanding feature of the book is its discussion of laboratory procedures, especially those which can be performed in the physician's own office. Details of technique are described, necessary apparatus and reagents are enumerated, and the plan and equipment of an office laboratory are discussed. Throughout the book the Author shows a keen insight into the needs of the doctor and the essentials of sound general practice. The book is highly recommended to all practitioners: to the beginner as a valuable guide in establishing good clinical habits; to the older man as a most practical bit of post-graduate instruction. R. K.

THE INJURED BACK AND ITS TREATMENT. Edited by JOHN D. ELLIS, M.D., with 7 Contributing Authors. Pp. 377; 17 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$5.50.

WRITTEN by outstanding authorities, this monograph is one of value. The subject is covered from the clinical orthopedic and neurosurgical angles. Details of routine examination and of treatment are given adequate coverage. The illustrations, tables and bibliography add much to the worth of this excellent treatise. G. W.

PHARMACOLOGY and THERAPEUTICS. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Late Professor of Materia Medica and Pharmacology, University of Edinburgh. Pp. 852; 66 illustrations. Twelfth Edition, thoroughly revised by C. W. EDMUNDS, A.B., M.D., Professor of Materia Medica and Therapeutics, University of Michigan, and J. A. GUNN, M.A., M.D., D.Sc., F.R.C.P., Professor of Pharmacology and Director of the Nuffield Institute for Medical Research, University of Oxford, Oxford, England. Philadelphia: Lea & Febiger, 1940. Price, \$6.50.

THE twelfth edition brings this standard text on pharmacology up to date so far as major advances in the last 4 years are concerned. Liberal additions have been made throughout the book, resulting in a total increase of about 50 pages. New chapters dealing with the sulfonamide group of drugs, benzedrine, and sex hormones have been included and the pages on vitamins have been practically rewritten. Unfortunately, deletions have not always kept pace with additions of new material, and some of the newer drugs of established value have been omitted. It is also to be regretted that the practical aspects of pharmacology have not received the increasing attention they merit, so that this book is becoming less useful to the practising physician. Despite these objections, Cushny's Pharmacology continues as one of our best texts on the subject available at present.

J. C.

CONVALESCENT CARE. Proceedings of the Conference held under the Auspices of the Committee on Public Health Relations of the New York Academy of Medicine, November 9 and 10, 1939. Pp. 261. New York: The New York Academy of Medicine, 1940.

THESE proceedings comprise data, opinions and advice on the subject of convalescent care that were contributed by 78 eminent physicians, hospital administrators and social and welfare workers who participated in the Conference. At the three sessions of the Medical Round Table there were discussed basic considerations of convalescent care (the physiology and psychology of convalescence, nutrition and convalescence, convalescence and chronic illness); convalescent care for various types of patients; psychosomatic aspects. The session of the Socio-economic Round Table considered problems of case finding, planning for the convalescent patient, care in the home, New York's convalescent day camp, difficulties in placement of certain types of patients in convalescent homes, and financing of convalescent care. At the concluding General Meeting summaries of the round table discussions were presented. Outstanding impressions which the book gives are: the many gaps in our scientific knowledge and the consequent need for study in the physiology and treatment of convalescence; the pathetically inadequate facilities in every phase of convalescent care; the great need for better integration of facilities for convalescent care with one another and with hospitals and the medical profession. The contents of this volume will prove to be not only interesting and informative to all its readers, but a challenge to those with any part in the function of a hospital.

R. K.

BIOCHEMISTRY OF DISEASE. By MEYER BODANSKY, Ph.D., M.D., Director of the John Sealy Memorial Laboratory and Professor of Pathological Chemistry, University of Texas School of Medicine, and OSCAR BODANSKY, Ph.D., M.D., Lecturer in Biochemistry, Graduate Division, Brooklyn College, etc. Pp. 684; 72 illustrations. New York: The Macmillan Company, 1940. Price, \$8.00.

BIOCHEMISTRY has become an indispensable part of the science and practice of medicine. But all too often the practitioner, long removed from laboratory and classroom, finds it difficult to understand the biochemical

aspects of disease. The present work is a systematic presentation of biochemistry as applied to disease. The book is well arranged, the chemical aspects of various organs and systems of tissue are discussed separately; emphasis is placed on facts of clinical significance. The work may be recommended as a well balanced, thoroughly modern presentation which will repay study and use.

B. L.

CLINICAL PRACTICE IN INFECTIOUS DISEASES. For Students, Practitioners and Medical Officers. By E. H. R. HARRIES, M.D., Lond., M.R.C.P., D.P.H., Medical Superintendent, North-Eastern Hospital (London County Council), etc., and M. MITMAN, M.D., Lond., M.R.C.P., D.P.H., D.M.R.E., Medical Superintendent, River Hospitals, etc. With a Foreword by W. ALLEN DALEY, M.D., Lond., F.R.C.P., D.P.H., Medical Officer of Health, London County Council.

THE text is a brief, often tabular, compilation of the essential facts of the familiar infectious diseases. Etiology, epidemiology, immunology, symptoms, differential diagnosis, therapy, and so on are the topics covered. The most recent advances in the production of active and passive immunity and in serotherapy are included. The opening chapters are devoted to general phases of infection and resistance, allergy in infection, transmission, the last chapter to control of contagious diseases in institutions. The work is adequately comprehensive, omits most debatable subjects, and is well designed for students and practitioners.

W. B.

A TEXTBOOK OF HISTOLOGY. By HARVEY ERNEST JORDAN, A.M., Ph.D., Professor of Anatomy and Director of the Anatomical Laboratories, University of Virginia. Pp. 690; 609 illustrations. Eighth Edition. New York: D. Appleton-Century Company, 1940. Price, \$7.00.

THE general plan of this edition remains unchanged. The number of illustrations is the same as in the preceding edition but there are about 50 pages less of text. The latter is due chiefly to the elimination of the chapters on histologic technique and the directions for laboratory work. This omission is an indication of the trend of the times in medical education and was decided on because of the shorter time devoted to histology in the medical curriculum and partly because work in technic is frequently a part of college activities in biology. The new figures are more illustrative than the old ones which they replace, and the book as a whole gives a well balanced and up-to-date account of human histology.

W. A.

PHYSIOLOGY OF MICTURITION. Experimental and Clinical Studies With Suggestions as to Diagnosis and Treatment. By ORTHELLO R. LANGWORTHY, LAWRENCE C. KOLB and LLOYD G. LEWIS, Sub-Department of Neurology and James Buchanan Brady Urological Institute, The Johns Hopkins University. Pp. 232; 49 illustrations. Baltimore: The Williams & Wilkins Company, 1940. Price, \$3.50.

IN this excellent monograph the authors have reviewed the experimental work of the past several decades concerning the physiology of urination. There is a complete discussion of the anatomy, physiology and nerve supply of the bladder. Of great value to the clinician and physiologist are the many case reports with important cystometrographic studies. Neurogenic disturbances of urination are described in detail.

This monograph is invaluable not only in thoroughly analyzing bladder dysfunction but in correlating this dysfunction as an aid to study and diagnosis of disease of the C.N.S.

B. H.

APPLIED PHARMACOLOGY. By HUGH ALISTER MCGUIGAN, PH.D., M.D., F.A.C.P., Professor of Pharmacology and Therapeutics, University of Illinois College of Medicine, Chicago. Pp. 914; 35 illustrations. St. Louis: The C. V. Mosby Company, 1940. Price, \$9.00.

THIS book might well have become a very important contribution to pharmacologic literature for it appears to have been conceived with the idea of furnishing a physiologic background for the action of drugs. Unfortunately, as written, it represents neither adequate physiology, adequate pharmacology nor adequate therapeutics. The very commendable idea of providing a physiologic basis for the subject has resulted often in stress of unimportant factors and the inclusion of completely irrelevant material. For example, 12 pages on the "Pharmacology of Respiration" (gaseous exchange in lungs, cellular respiration, cytochrome, glutathione, oxygen debt, oxygen dissociation curves, metabolic energy, and respiratory quotient) leads up to a scant 10 lines on "Oxygen as a Therapeutic Agent." It quickly becomes evident to the reader that the physiologic aspects are too often merely included and not correlated.

The treatment of the pharmacologic material is marred by omissions, errors and contradictions with which the book is replete. For example, while literature as late as 1940 is quoted (sulfathiazole), new drugs such as dihydrotachysterol, corticosterone, choline derivatives, cobra venom, stilbesterol, mercurin have not been included; and new drug forms such as adrenalin in oil, adrenalin for inhalation, mercurial suppositories have not been mentioned. The section on blood transfusions omits such blood substitutes as plasma, lyophilized serum, placental or cadaver blood.

Insofar as the "applied pharmacology" sections are concerned, clinicians will probably not be satisfied with $1\frac{1}{2}$ pages on sulfanilamide, 5 lines on the treatment of hypertension and a lack of definiteness in numerous sections, such as the following: five therapeutic uses of diaphoretics are listed followed by this comment, "In some of these conditions diaphoretics are advisable and in others their use is of doubtful value."

The order of the subject material is often inexplicable: agranulocytosis is considered under "blood volume," blood transfusion under "coagulants." A chapter on amines separates hypnotics and sedatives from the opium series and the sympathomimetic amines are discussed 41 pages later. The chapter entitled "The Chemotherapy of Syphilis" begins with mercury, arsenic, and iodides, followed by selenium, tellurium, antimony and silver before bismuth is mentioned; this chapter then ends with 18 other metals (including iron and lead) none of which has ever been used in syphilotherapy.

J. C.

MEDICAL WORK OF THE KNIGHTS HOSPITALLERS OF SAINT JOHN OF JERUSALEM. By EDGAR ERSKINE HUME, Lieutenant-Colonel, Medical Corps, U. S. Army; Knight of Honor and Devotion of the Sovereign Military Order of Malta. Foreword by His Most Eminent Highness FRA LUDOVICO CHIGI-ABANI, Prince Grand Master of the Sovereign Military Order of Malta. Preface by Lieutenant-General SIR ALDO CASTELLANI, K.C.M.G., Count of Chisimaio, Magistral Knight of the Sovereign Military Order of Malta; Professor of the Universities of Rome, London and Louisiana. Pp. 371; 130 illustrations. Baltimore: The Johns Hopkins Press, 1940.

THE history of the Knights of Malta, as the Order is commonly called, is indeed fascinating and no one could better discuss its medical aspects than Colonel Hume, himself a member of the Order. As the book is, in fact, a history of the first military surgeons, published while the world writhes in the grip of another great war, it assumes further significance.

The story begins with the foundation of the Order at Jerusalem in the

eleventh century and follows the Knights down through the centuries to the present. The book is concerned mainly with the medical activity of the Order, which was indeed its foremost interest, and the reader is provided with a wealth of documented material pertaining to the practice of medicine and surgery, hospital construction, and nursing. For purposes of completeness, however, the author includes much of the economic and political development of the Order which is equally interesting and important, for during the last millenium the Knights have played a rôle in almost every great drama of the Western World.

Today, even as bombs rain on their former home, the Knights are engaged in medical work the world over and Colonel Hume has given this work well deserved recognition. A foreword by the present Grand Master of the Order and the liberal use of photographs and documents add further to the highly interesting monograph. F. M.

FELDCHIRURGIE: Leitfaden für den Sanitätsoffizier der Wehrmacht.

Written by 11 German Medical Officers and edited by DR. H. KÄFER, Generaloberstabsarzt. Pp. 354; 58 illustrations. Dresden: Theodor Steinkopff, 1940. Price, Rm. 9.

THE title, "Field Surgery," applies to the surgery of the front, that in general ends at the entrance of the field hospital from which the wounded are sent to the rear. The purpose of the book is to supply the needs of the young medical officer of the fighting unit, who is so often thrown on his own resources, and to the young medical officer in advanced dressing stations. The subject matter offers "not theories or controversial opinions, but accepted measures and methods of war surgery, proved in the world war and further tried in the present conflict." (The book was published in March 1940.) Part I (General Section) includes chapters on the organization of the medico-military service and fundamentals of medical tactics; war weapons and their effects; transportation and transportability of wounded; Roentgen ray service in the field; general surgical technique at the front; appraisalment of war wounds and first aid; infection and war wounds; collapse and shock; relief of pain at the front; hemorrhage, hemostasis and blood replacement. Part 2 (Special Section) deals with specific types of wounds, under the headings of wounds of the skull; the face, the jaw and mouth; the neck; the chest; the abdomen; the urogenital tract; the back, spine and cord; the extremities. The material has, in the main, been well handled, in a concise but adequate fashion. (There is no mention of plasma transfusions.) The book itself is neat, compact, of pocket size. It is freely recommended to military surgeons who read German. Those entrusted with the preparation of our own service manuals will find here much that is useful. R. K.

THE CHINESE WAY IN MEDICINE. By EDWARD H. HUME. Pp. 189; illustrated. Baltimore: The Johns Hopkins Press, 1940. Price, \$2.25.

THIS book is a brief but interesting summary of Chinese medicine. Although some factual material is included, the monograph is intended not as a complete history but rather as a general inquiry into the background, development and contributions of Chinese medicine.

The study is divided into three parts. In the first, a discussion of the influence of the early philosophers on Chinese medicine, in the development of scientific thought is seen to have been hampered by their rigid adherence to tradition. The second part takes up the lives of certain great Chinese physicians, both in legend and in written history, and is enlivened by the inclusion of a number of folk stories concerning their activities. The remainder of the book deals with the contributions made by the Chinese to general medical knowledge.

The author has presented a most readable and lucid picture of the Chinese mentality and thereby clears up many of the apparent paradoxes of their slow scientific development. F. M.

MULTIPLE HUMAN BIRTHS. Twins, Triplets, Quadruplets and Quintuplets, By HORATIO HACKETT NEWMAN, PH.D., Sc.D., Professor of Zoölogy. University of Chicago. Pp. 214; illustrated. New York: Doubleday, Doran & Co., Inc., 1940. Price, \$2.50.

For the United States the ratio of twins to single births is 1 to 86, or 1.15%, of which about one-fourth are 1-egg twins and three-fourths 2-egg twins. The occurrence of triplets, quadruplets and quintuplets is much less frequent and may be expressed roughly "if one twin birth occurs for each 86 single birth, then one triplet birth occurs for each 86 twin birth, and one quadruplet birth occurs for each 86 triplet birth: in other words, if the ratio of twins to single births is 1 to 86, that of triplets to single births is 1 to 86² and that of quadruplets to single births 1 to 86³. Of quintuplets, there are records of at least 60 cases, but of sextuplets only 6 are mentioned in medical literature.

The methods of twinning are discussed. Bi-ovular twins are independent of one another and no more closely resemble one another than siblings. They result from the accidental liberation of 2 eggs that may be separately fertilized, even by different fathers, and have nothing in common except simultaneous gestation. The uni-ovular or 1-egg twins result from the separation of the two halves of 1 egg after its first division. If the separation is incomplete, double monsters or "Siamese Twins" may result. Triplets may result from a second division of one half, and quadruplets from a second division of both halves, as is habitual in the armadillo. Sextuplets result from second division of both halves and a third division of one. If any one of the resulting embryos die, as was the case of the "Dionne quints," a fleshy body may be expelled, and the five remaining embryos remain and develop. Twins are more precisely alike; 2 of triplets, of the same sex, must be much alike, the third may be very different and of a different sex. Quadruplets from 1 egg must be much alike and of the same sex, as also are most quintuplets and sextuplets derived from 1 egg.

Twins are disadvantageous to the race for various reasons given. They seem to be slightly less intelligent than other people as more of them fail to qualify for admission to school than siblings.

The psychologic studies made by the author and his associates are interesting. J. McF.

THE THEORY AND PRACTICE OF ANAESTHESIA. By M. D. NOSWORTHY, M.A., M.D., B.Ch. (CANTAB.), Anesthetist to Westminster Hospital and Grosvenor Hospital for Women, late Senior Resident Anesthetist, St. Thomas's Hospital; with a Foreword by I. W. MAGILL, M.B., B.Ch. (BELFAST), Senior Anesthetist to Westminster Hospital, Anesthetist to Brompton Hospital for Consumption and Diseases of the chest. Pp. 223; 35 illustrations. New York: Chemical Publishing Company, 1940. Price, \$4.25.

THIS little 200-page book is a real contribution to anesthesia, but particularly to anesthesia in the United States. American works have tended to stress the physiologic and pharmacologic aspects of anesthesiology, whereas this book emphasizes the technical problems of the subject, an approach characteristic of the English school. Practical aspects of the administration of anesthetic agents are stressed throughout, with full attention to all methods from open drop to endotracheal techniques. Regional anesthesia is not covered, with the exception of one chapter on spinal anesthesia.

Of interest to American readers is the full discussion of chloroform, for

there can be no doubt but that this agent has a place in the anesthetist's armamentarium.

Since its first appearance in 1935, the book has been reprinted twice with but few changes, and one can criticize some of the physiologic principles evoked. An ideal combination in a book on anesthesia would be the fusion of the American trend towards physiology with the English insistence upon technical skill.

R. D.

SYNOPSIS OF MATERIA MEDICA, TOXICOLOGY AND PHARMACOLOGY. For Students and Practitioners of Medicine. By FORREST RAMON DAVISON, B.A., M.Sc., Ph.D., M.B., Assistant Professor of Pharmacology in the School of Medicine, University of Arkansas, Little Rock, Ark. Pp. 633; 45 illustrations (4 in color). St. Louis: The C. V. Mosby Company, 1940.

THIS book is a pharmacologic text that can be recommended to the practising physician. It is accurate, up-to-date, and concise. While it does not pretend to be an encyclopedia of pharmacologic information, it does contain the essential actions, uses, and toxic manifestations of all useful drugs. There is a good chapter on prescription writing, and a shorter one dealing with toxicology. Numerous practical prescriptions are given throughout the text, a feature which should appeal to many physicians.

The book is well printed and indexed but it is regrettable that so few original illustrations have been used, especially since most of the illustrations have now appeared in three pharmacology texts published within the year.

J. C.

NEW BOOKS.

Diseases of the Digestive System. Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine, Rush Medical College of the University of Chicago; Attending Physician, Michael Reese Hospital; Consulting Physician, Cook County Hospital, Chicago. (Fifty Contributors.) Pp. 952; 176 illustrations. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.

The Role of the Liver in Surgery. By FREDERICK FITZHERBERT BOYCE, B.S., M.D., Diplomate of the American Board of Surgery; Fellow of the American College of Surgeons; Visiting Surgeon: Charity Hospital of Louisiana at New Orleans, French, Mercy, Southern Baptist Hospitals, Hotel Dieu and Touro Infirmary. Pp. 365; 44 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.00.

Plague on Us. By GEDDES SMITH. Pp. 365; illustrated. New York: The Commonwealth Fund, 1941. Price, \$3.00.

Radiologic Physics. By CHARLES WEYL, S. REID WARREN, JR., and DALLETT B. O'NEILL, Moore School X-Ray Laboratory, Moore School of Electrical Engineering, University of Pennsylvania. With a Foreword by EUGENE P. PENDERGRASS, M.D., Director of the Department of Radiology, University of Pennsylvania. Pp. 459; over 160 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.50.

Mechanisms of Biological Oxidations. By DAVID E. GREEN, Senior Beit Memorial Research Fellow, Institute of Biochemistry, University of Cambridge (Cambridge Biological Studies, General Editor, C. H. WADINGTON). Pp. 181; 22 figures. Cambridge: The University Press, 1940. New York: The Macmillan Company, 1941. Price, \$2.75.

Die Appetitlosigkeit im Kindesalter. By JULIUS SURÁNYI, Oberarzt am Stefanie-Kinderspital. Pp. 128. Basel: S. Karger, 1940. Price, Sfr. 6.

The Medical Clinics of North America. Vol. 25, No. 1 (*Chicago Number, January, 1941*). Pp. 302; 35 illustrations. Philadelphia: W. B. Saunders Company, 1941.

The first half of this number presents 9 articles on the diagnosis and treatment of pains of various origins in several parts of the body. The remaining 11 articles are devoted to treatment of common ailments—mostly medical.

Electrocardiography in Practice. By ASHTON GRAYBIEL, M.D., Instructor in Medicine, Courses for Graduates, Harvard Medical School; Research Associate, Fatigue Laboratory, Harvard University; Assistant in Medicine, Massachusetts General Hospital, and PAUL D. WHITE, M.D., Lecturer in Medicine, Harvard Medical School; Physician, Massachusetts General Hospital, in charge of the Cardiac Clinics and Laboratory. Pp. 319; 272 figures. Philadelphia: W. B. Saunders Company, 1941. Price, \$6.00.

Temperature—Its Measurement and Control. By Numerous Authors Sponsored by the American Institute of Physics. Pp. 1375. To be published by Reinhold Publishing Corporation, 330 West 42d St., New York City. Price, \$11.00. An Appendix of 25 reference tables is included and may be purchased separately bound for \$1.00 per copy.

Studies from The Center for Research in Child Health and Development, School of Public Health, Harvard University. *III. The Growth of Bone, Muscle and Overlying Tissues as Revealed by Studies of Roentgenograms of the Leg Area.* By HAROLD C. STUART, M.D., PENELOPE HILL and CONSTANCE SHAW. Vol. 5, No. 3, Serial No. 26 (Monographs of the Society for Research in Child Development). Pp. 190 and Appendix (27 pages). Washington, D. C.: Society for Research in Child Development, National Research Council, 1940. Price, \$1.25.

Biological Aspects of Infectious Disease. By F. M. BURNET, M.D., Assistant Director, Walter and Eliza Hall Institute, Melbourne. Pp. 310; 9 figures and 4 plates. Cambridge: The University Press. New York: The Macmillan Company, 1940. Price, \$3.75.

NEW EDITIONS.

The Extra-Ocular Muscles. A Clinical Study of Normal and Abnormal Ocular Motility. By LUTHER C. PETER, A.M., M.D., Sc.D., LL.D., Professor Emeritus of Diseases of the Eye in the Graduate School of Medicine of the University of Pennsylvania; Consulting Ophthalmologist in the Rush Hospital for Consumption and Allied Diseases, The Friends' Hospital for Nervous and Mental Diseases and the Roxborough Memorial Hospital. Pp. 368; 147 illustrations and 5 colored plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$4.50.

Modern Drug Encyclopedia and Therapeutic Guide. Presenting descriptions of 11,114 modern, non-pharmacopeal, ethical medicinal preparations in 15,629 forms, comprising: 3,421 drugs and chemicals, 663 biologicals, 691 endocrines, 2,270 ampoule medicaments, 3,190 individual and group allergens and 879 miscellaneous products. For the Use of Physicians, Dentists, Pharmacists, and Medical Students. By JACOB GUTMAN, M.D., PHAR.D., F.A.C.P., Director, Brooklyn Diagnostic Institute; Consulting Physician, Manhattan General Hospital, New York, the Riverdale, Shore Road, Williamsburg Maternity and Borough Park General Hospitals of Brooklyn. Pp. 1644. Second Edition. New York: New Modern Drugs, 1941. Price, \$7.00.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF
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BILATERAL CORTICAL NECROSIS OF THE KIDNEYS.

BILATERAL cortical necrosis or symmetrical cortical necrosis of the kidneys are terms used to indicate a pathologic entity of obscure etiology characterized by more or less complete and uniform necrosis of the cortex of both kidneys, including the columns of Bertin. This interesting lesion was first recognized and described in a case reported by Juhel-Rénoy³⁹ in 1886. Ash,² in 1933, made a complete survey of the literature up to that time and was able to find 42 cases which he considered authentic, as well as 18 in which the clinical course or pathologic findings or both were suggestive but not conclusive. He also reported 2 cases of his own. Including the latter, 45 new cases have been reported in the 7 years which have elapsed since Ash's review of the literature. The fact that more cases of bilateral cortical necrosis of the kidneys have been reported in the last 7 years than in the preceding 47 does not necessarily indicate an increasing incidence of the disease, but it definitely points to an increasing interest in and recognition of this peculiar lesion of the kidneys.

In addition to the cases already mentioned there have been reported in recent years two groups in which chemical poisoning produced a form of renal necrosis similar in many respects to bilateral cortical necrosis of the kidneys of unknown cause. Barber,⁴ in 1934, reported 5 industrial fatalities among workers exposed to the inhalation of dioxane fumes (di-ethylene dioxide, the anhydride of di-ethylene glycol). Postmortem examination in 3 of these cases revealed patchy hemorrhagic necrosis of the renal cortex and central necrosis of the liver lobules. In the second group, reported some 3 years ago, death followed the ingestion of an elixir of sulphanilamide (Massengill). These deaths were attributed to the fact that the elixir contained di-ethylene glycol as a solvent. In these cases the changes in the kidneys consisted of an intense hydropic degeneration of the renal tubular epithelium

followed in some instances by a patchy hemorrhagic necrosis of the renal cortex.^{8,24,48} There was also marked hydropic degeneration of the central cells of the liver lobules. Similar hydropic degeneration of the liver and kidneys has been produced experimentally in animals by the administration of either dioxane^{53b} or di-ethylene glycol.^{10,24,25,42} The constant presence of conspicuous lesions in the liver as well as in the kidneys in both groups of human cases distinguishes them from all others of symmetrical renal cortical necrosis. Moreover, the fact that careful investigation has clearly established the etiologic agents sets these cases apart as groups by themselves, representing the effects of dioxane poisoning in the first instance and of di-ethylene glycol poisoning in the second. For these reasons these two groups of cases will be omitted from detailed consideration in this review and attention will be devoted exclusively to the cases of bilateral necrosis of the renal cortex in which no such clear-cut etiologic factors are apparent.

While a few cases, diagnosed clinically as bilateral cortical necrosis of the kidneys, have been reported with recovery,^{14,27,49,65} it is our intention to analyze only those in which the diagnosis is established beyond doubt by postmortem examination and adequate description of the pathologic changes. If this criterion is applied it is necessary to exclude 5 of Ash's 42 authentic cases.² Moreover, 12 cases reported more recently by de Navasquez^{53a} do not lend themselves to analysis since the cases are not individually protocolled. However, 1 case reported in 1923 by Bamforth³ and not tabulated by Ash is added here as an authentic case. Thus, it is possible to base a description of the clinical and pathologic features of the disease on an analysis of 71 cases. This description will be followed by a summary of the experimental methods by which the renal lesions appear to have been reproduced in animals, and finally by a discussion of the etiology and pathogenesis of bilateral cortical necrosis of the kidneys as it occurs in man.

From the point of view of clinical history, the 71 cases fall naturally into two groups, those in which bilateral cortical necrosis of the kidneys occurred at the termination of pregnancy and those in which there was no association with pregnancy. The former group, comprising 48 cases, is set out in Table 1, while the cases of renal necrosis not associated with pregnancy and numbering 23 are shown in Table 2. The numerical predominance of the first group over the second is due largely to an even greater predominance of such cases in the literature prior to 1933. Of the 33 cases reported since that time and analyzed here, 17 occurred in males or non-pregnant females. Thus, it is no longer possible to agree with statements such as that of de Navasquez^{53a} that there is an "almost invariable association with pregnancy." While bilateral cortical necrosis of the kidneys may occur at the termination of pregnancy, or may be associated with a variety of other diseases or may appear as a primary disease *per se*, the renal lesions themselves are of identical character in all cases, as are also the clinical signs and symptoms referable to these lesions. Therefore, it is necessary to separate the groups only insofar as differences exist in the clinical background upon which the signs and symptoms of bilateral cortical necrosis of the kidneys make their appearance. Anuria or extreme oliguria marks the onset of the disease. From this point onward the clinical course is virtually the same in all fatal cases and for this reason we shall deal with all

TABLE 1.—FORTY-EIGHT CASES OF BILATERAL CORTICAL NECROSIS OF KIDNEYS ASSOCIATED WITH PREGNANCY.

Associated pregnancy.			Bilateral cortical necrosis of kidneys.							Remarks.						
Author Ref. No.	Age.	Month of termination of pregnancy.	Accidental hemorrhage.	Other evidence of pre-eclampsia.	Eclamptic convulsions.	Onset of anuria.*	Days of anuria.		Abnormal urinary constituents.		Nitrogen retention.	Blood pressure.	Edema.	Renal pain.	Vomiting.	Coma or drowsiness.
							Partial.	Complete.								
6	32	6	..	+	..	0	4	Almost	+	+	140/86	0	+	+	+	Headaches and impaired vision before delivery.
7	36	?	0	?	0	7	+	..	200/130	0	+	+	+	Headaches before delivery; renal endarteritis.
11	36	6	0	0	6	7	+	..	150/?	+	+	Edema of eye grounds.
12	23	7	0	0	0	5	+	+	+	+	Credé removal of placenta; terminal convulsions.
13	28	8	+	0	1	3	+	..	145	+	+	Renal decapsulation.
15	23	5	+	0	4	5	+	+	135	+	+	+	+	Chr. nephritis; headaches; purulent endometritis.
16	30	9	+	0	0	11	+	+	118/50	+	+	+	+	Cesarean section.
17 (1)	37	7	0	0	12	3	+	..	120/80	+	+	+	+	Poor vision; induced labor; extreme collapse.
17 (2)	39	7	0	..	0	0	11	1	+	+	+	0	+	Infarction of placenta.
17 (3)	24	?	+	0	1	6	+	+	..	+	+	+	+	Headaches and impaired vision; Cesarean section.
17 (4)	33	Prem.	+	..	+	0	14	7	+	+	115/75	+	+	+	+	Headaches and blurred vision; renal decapsulation.
18	24	?	+	+	+	0	11	Almost	+	+	180/120	+	+	+	+	Abnormal fundi; accidental hemorrhage; hysterectomy.
19	39	7	+	..	+	0	3	3	+	+	140/80	+	+	+	+	Visual disturbances; infected uterus; adrenal necroses.
23	33	?	0	8	7	+	+	152/108	..	+	+	+	Placenta previa; hemorrhage; renal decapsulation.
26a	32	7	0	0	0	0	0	4.5	..	+	150	..	+	+	+	Chr. nephritis; retinitis.
26b	35	9.5	..	+	+	0	0	7	..	+	..	+	+	+	+	Impaired vision; induced labor; splenic infarcts.
28	29	8	0	7	Almost	+	+	..	+	+	+	+	Headaches before delivery; renal endarteritis.
30	35	?	0	4	4	+	+	..	+	+	+	+	Chr. nephritis; headaches; poor vision; endometritis.

TABLE 2.—TWENTY-THREE CASES OF BILATERAL CORTICAL NECROSIS OF KIDNEYS NOT ASSOCIATED WITH PREGNANCY.

Author Ref. No.	Age.	Sex.	Associated disease.	Bilateral cortical necrosis of kidneys.										Remarks.
				Days of anuria.		Abnormal urinary constituents.	Nitrogen retention.	Blood pressure.	Edema.	Renal pain.	Vomiting.	Coma, drowsiness.		
				Partial.	Complete.									
1	13.5	M	Pulmonary tuberculosis	0	2	+	+	120/85	+	+	+	+	Mural thrombi in heart and aorta.	
2 (1)	25	M	No previous history of ill health	0	17	+	+	Bacteria in vessels of spleen, liver, pancreas.	
2 (2)	32	M	No previous history of ill health	12	7	+	+	Kidney the only site of disease.	
3	37	M	Dysentery (?) 6 days; influenza 1 mo. previous	0	3	+	+	150/92	+	+	+	+	No path. or bact. confirmation of dysentery.	
5	35	M	Chr. alcoholic with acute alcoholism	1	5	+	+	110/25	+	+	+	+	Intense cloudy swelling of liver.	
20	38	M	No previous history of ill health	0	12	+	+	Abdom. pain, vomiting, diarrhea, pancreatitis.	
21	22	F	Automobile accident; extreme shock	3	0	+	+	132/68	+	+	+	+	Lungs typical of shock; ruptured liver.	
22 (1)	40	F	Ingestion of almond extract	0	3.5	+	+	160/85	+	+	+	+	Edema of fundi; central necrosis of liver.	
22 (2)	53	F	Hypertension; chr. alcoholic; Wassermann 4+	0	6	+	+	160/80	+	+	+	+	Syphilitic aortitis; central necrosis of liver.	
22 (3)	23	M	Chr. alcoholic	5.5	0	+	+	164/70	+	+	+	+	Edema of fundi; central necrosis of liver.	
31	35	M	Past and present thrombocytopenic purpura	0	8	+	+	Necrosis of spleen with thrombosed arteries.	
39	16	F	Scarlet fever 10 days before anuria	0	5	+	+	150/40	+	+	+	+	Terminal convulsion.	
44	48	M	Malarial treatment for syphilis	0	0	+	+	Unexpected death; syphilitic aortitis and meningitis.	
45 (1)	22	F	Psychosis; refused food and drink for 2 weeks	0	11	+	+	Extreme dehydration; petechiae of brain.	
45 (2)	46	F	Pneumonia with acute mania	11	0	+	+	120/60	+	+	+	+	Edema of fundi; ulcers of esophagus.	
46	35	M	Local anesthetic for nasal operation	0	7	+	+	Hb. 11%; liver necrosis.	
56	15	M	Bitten by cobra 26 days before death	26	0	+	+	Multiple hemorrhagic splenic infarcts.	
67	46	M	Laryngeal and tracheal diphtheria	0	8	+	+	Adrenal necrosis; petechiae of brain.	
69	50	F	Hypertension; taking thyroid extract	0	6	+	+	Terminal convulsions; uremic breath.	
73	17	M	Tonsillitis and nephritis 1 mo. before	15	2	+	+	130/7	+	+	+	+	Central necrosis of liver.	
78 (1)	13	F	Tonsillitis and joint pains	0	10	+	+	95/7	+	+	+	+	Pneumonia with abscess formation at autopsy.	
78 (2)	64	M	Chr. pulmonary disease; ac. bronchopneumonia	0	4	+	+		
79	14	F	Pneumonia with camphor injections for 3 days	0	4	+	+		

cases in a single account of the clinical features of symmetrical necrosis of the renal cortex.

Clinical Background of Bilateral Cortical Necrosis of the Kidneys. *Pregnancy.* The 48 cases of bilateral cortical necrosis of the kidneys detailed in Table 1 were associated with pregnancy. The ages of these patients are distributed throughout almost the whole child-bearing period. The youngest patient was 19 years, the oldest 48, but almost two-thirds of the cases occurred in women from 30 years upward and exactly one-third in the period from 30 to 35 years inclusive. The number of previous pregnancies varied from zero to 15, and appeared to have no bearing on the occurrence of renal necrosis. The pregnancies in association with which symmetrical necrosis of the kidneys occurred were terminated with striking frequency by premature delivery and resulted in stillbirth in all cases but 1 (twins).^{36a} Among 36 cases in which the month of pregnancy is recorded, gestation was terminated prematurely in 33 cases, usually in the fifth to eighth month. Premature delivery was explained in 21 cases by premature separation of the placenta and in 8 other cases by the occurrence of pre-eclamptic toxemia. Convulsions occurred in 12 cases before the beginning of anuria. Only 1 of these patients had had convulsions at the end of a previous pregnancy. Headache or disturbances of vision or both were mentioned as occurring in one-half of the cases, frequently beginning a week or more before delivery. It is noteworthy that these symptoms were conspicuous by their absence among the cases of bilateral cortical necrosis of the kidneys not associated with pregnancy. Only 1 patient¹⁵ was said to have suffered from nephritis in the final pregnancy, and this patient as well as 2 others,^{26a,30} had had nephritis previously. Cæsarean section was performed in 4 cases,^{16,17,43,50} a version in 1,⁵⁸ a Credé removal of the placenta in 1,¹² and the membranes were artificially ruptured in 6 cases, with the definite development of surgical shock in 1 of these.⁶⁵ Postpartum infection of the uterus was rare, occurring in only 6 cases, in 3 of which^{38,41} it was a sequel to induced abortion. In 2 cases⁴¹ there was infection of abdominal operative wounds. However, in all cases of infection, anuria appeared before the infection was detected clinically. The time of appearance of anuria was noted in 45 of the 48 cases. It began on the day of delivery in 36 cases, within 3 days after delivery in 5 cases, and preceded delivery in 4 cases. All of the 4 latter patients^{41,47,66} had shown signs of some form of toxemia before anuria commenced.

Conditions Other Than Pregnancy. The 23 cases of bilateral cortical necrosis of the kidneys not associated with pregnancy are shown in Table 2. The patients were males in 15 instances and females in 8. Their ages were distributed almost uniformly through the second to fifth decades with only 3 cases over the age of 50. The youngest patient was 13 years old and the oldest 64. There was no significant difference between the two sexes in age distribution. Symmetrical renal necrosis occurred in association with a variety of apparently unrelated conditions in 20 cases, and it appeared also in 3 cases in the absence of any associated disease and without any clue as to a possible etiologic factor. The renal lesions occurred in 9 cases during the course of various infections such as scarlet fever,³⁹ diphtheria,⁶⁷ tonsillitis,^{73,78} pneumonia,⁴⁵ pneumonia with camphor injections,⁷⁹ tuberculosis,¹ thera-

peutic malarial infection,⁴⁴ and dysentery.³ Evidence of absorption of materials which might be interpreted as toxic was present in 8 cases. Such substances included camphor, injected during the course of pneumonia,⁷⁹ alcohol,^{5,22} local anesthetic employed for a nasal operation,⁴⁶ almond extract,²² cobra venom,⁵⁶ and thyroid extract administered for postoperative hypothyroidism.⁶⁹ In 1 case there was an associated nephritis.⁷³ Moderate hypertension was observed in 3 cases.^{22,69,73} Renal necrosis occurred in 1 case in association with thrombocytopenic purpura;³⁴ in another it was associated with extreme shock following an automobile accident,²¹ and in a third case it followed extreme dehydration of 2 weeks' duration due to refusal of the patient to eat or drink.⁴⁵ In 3 cases no antecedent event of possible causal significance was mentioned.^{2,20}

Clinical Features of Bilateral Cortical Necrosis of the Kidneys. Regardless of the clinical background upon which bilateral cortical necrosis of the kidneys makes its appearance, the course of the disease after the onset of anuria is essentially the same in all cases. Therefore, we shall consider together all of the 71 cases shown in Tables 1 and 2 insofar as the clinical features of symmetrical renal necrosis are concerned.

Anuria or extreme oliguria marks the onset of the disease. In 29 of the 71 cases this was accompanied by pain or tenderness either in the epigastrium or loins, or beginning in the epigastrium and radiating to the loins. In some instances the pain radiated along the course of the ureters. Complete anuria persisted in some cases from the first day until death, but in others it was preceded by a period of extreme oliguria. In those patients who survived for the longest times, a period of complete anuria was followed by the excretion of small quantities of urine. The total duration of the disease varied within rather wide limits. Two patients died on the second day of urinary suppression,^{1,41} while 1 patient suffered from anuria followed by oliguria for a total of 32 days before death.⁴¹ Of the 71 patients, 52 died in 4 to 12 days. Among the 52 cases in which urine was obtained for examination it contained in 48 cases abnormal constituents, notably quantities of albumin in 47 cases, white blood cells in 26, red blood cells in 22, and hyaline or granular casts in 19 cases. Several authors have noted that the small samples of urine obtained just before the onset of complete anuria were grossly bloody, a point emphasized as diagnostic by Kellar and Arnott⁴¹ and by Gibberd.²⁷ Various chemical examinations of the blood were carried out in 29 cases and in every instance yielded evidence of progressive nitrogen retention. The terminal level of the non-protein nitrogen, when reported, varied from 85 to 356 mg. per 100 cc., the terminal creatinine content ranged from 3.5 to 26 mg. per 100 cc., and the blood urea from 108 to 533 mg. per 100 cc. Headache and blurring of vision occurred only in those patients who had been pregnant and in most cases these symptoms were present before the onset of anuria. Examination of the eyegrounds in 13 cases revealed abnormalities in 9 instances consisting of edema of the disks or albuminuric retinitis, or both. In a few instances some tortuosity of retinal vessels was described. Edema of the dependent parts, followed in some instances by slight generalized edema, was observed in 28 of the 71 cases. The exact time of the appearance of edema was not stated in

every case, but there were some patients in whom edema first appeared after the onset of anuria. Blood pressure readings taken after the onset of anuria revealed no characteristic trend, except for a terminal fall in blood pressure in those cases where it was followed throughout the illness. The temperature in the majority of cases varied from 99° to 101° F. One patient had fever reaching 105° and in another the temperature rose to 106°. ⁴⁵ One of these had lobar pneumonia and the other became markedly dehydrated because of refusal to eat or drink. Leukocyte counts, when made, usually showed a leukocytosis ranging from 14,000 to 40,000. Almost without exception the patients were described as remaining in a state of extraordinary mental clarity until a day or two before death. It is true that some of the pregnant patients who had suffered convulsions at the time of delivery remained comatose during the first 1 or 2 days of anuria, but after this time these patients, as well as the others, were mentally clear almost to the end. Some degree of drowsiness occasionally passing over into coma, and sometimes associated with uremic twitchings or frank convulsions, were described as a terminal development in 31 of the 71 cases.

Thus the clinical course of most of the fatal cases of bilateral cortical necrosis of the kidneys is practically that which follows extirpation of the kidneys. It should be borne in mind, however, that symmetrical renal necrosis could quite conceivably occur to an extent sufficient to cause a period of oliguria or anuria, but not sufficient to exclude the possibility of restoration of function in the non-necrotic portions of the cortex with recovery of the patient. ^{14,27,41,49,54,55,65,76}

Pathologic Features of Bilateral Cortical Necrosis of the Kidneys. In the great majority of cases, the important pathologic changes are confined to the kidneys. The kidneys are slightly enlarged, somewhat swollen in appearance, and softer in consistency than normal. The capsule is usually of normal thickness and strips with ease leaving a perfectly smooth surface. A few cases have been reported in which the renal capsules were somewhat thickened and slightly adherent, while the kidneys themselves had finely granular surfaces and were not appreciably enlarged. ^{11,15,28,30,47,56,65,72}

As the name implies, the essential lesion of bilateral cortical necrosis of the kidneys is found within the renal cortex. Comparison of the descriptions of the characteristic renal changes as observed in the reported cases reveals certain differences in detail between different cases; but it is apparent that the lesions of the kidneys in all instances are of the same general character, representing ischemic necrosis of the renal cortex of varying degrees of severity. The least extensive renal lesions give the appearance of multiple small infarcts scattered throughout the cortex of both kidneys. With involvement of somewhat greater degree, there are numerous closely set infarct-like lesions of the cortex which in some places coalesce to form irregular bands of necrosis parallel to the cortical surface. In most cases the necrosis is even more widespread, so that the appearance of individual infarcts is lost, and almost the whole cortex, including the columns of Bertin, is rendered necrotic. However, even in such cases, scattered radial streaks of more or less intact cortical tissue separate the completely necrotic areas, indicating that the large necrotic areas are probably formed by the coalescence of innumerable small areas of ischemic

necrosis. Nevertheless, these different degrees of involvement do not represent stages in a chronologic sequence of events. It can only be stated that the extent of the necrosis varies from case to case. As might perhaps be expected, the least extensive lesions are frequently found in those patients who survive for the longest time, while extremely widespread necrosis is found in many patients who survive for only a few days.

Viewed from the surface of the kidney, the areas of necrosis in any given case have the same appearance everywhere, and appear to be of the same age. Recently necrotic areas show up on the external surface as red patches mottled with yellow, but in slightly older lesions the yellow color becomes predominant although a deep red peripheral zone remains. Such areas may be discrete, or may be so numerous as to coalesce in many places, or the whole surface of the kidney may be affected so that it is everywhere mottled or marbled with irregular red and yellow patches. Necrosis may be so extensive and complete that the whole kidney surface has a tawny yellow color, with only scattered flecks of red.

The cut surface of the kidney bulges slightly and the thickness of the cortex is somewhat increased. The infarct-like areas of necrosis are confined to the cortex and lie just beneath the surface, separated from it by an extremely thin layer of intact tissue, and extending for a variable distance towards the medulla. In a small number of cases,^{41, 53a, 73} early hemorrhagic necrosis has been described, but in most of the cases analyzed the necrosis was evidently of longer standing and lacked this hemorrhagic character. In cases of the latter kind, each area of necrosis possesses a yellow opaque center bordered by a narrow deep red zone which separates it from the surrounding normal tissue and passes through the thin subcapsular layer of intact tissue. Coalescence of individual areas of necrosis may obliterate the intervening red zones so that a solid yellow band of necrosis is formed, interrupted at long intervals by narrow red streaks. Necrosis of this extent may reach so close to the capsular surface that no peripheral red zone is distinguishable, although the inner margin of the necrotic band is clearly marked by a deep red line which is frequently described as being distinctly jagged or dentate. Areas of necrosis in the columns of Bertin have a similar yellow opaque appearance and are likewise limited by a peripheral zone of red. Usually the necrosis, even though very extensive, does not involve more than the outer half to two-thirds of the cortical layer but may involve almost its whole thickness down to the bases of the pyramids. In 3 cases^{41, 50, 65} the medullary tissue immediately adjacent to the cortex was also necrotic in places but in all other cases the medulla was entirely normal in appearance or merely hyperemic.

The grossly visible renal arteries and veins are notably free from occlusion of any form in almost every case, but non-occlusive arteriosclerotic plaques in the larger renal arteries have been described in 3 cases^{7, 28, 37} and thrombosis of the renal veins in 2 others.^{62, 70} The renal pelvis and peripelvic tissues as a rule show no gross alterations, but in a few instances petechial hemorrhages in the mucous membrane of the pelvis are mentioned.^{22, 38, 79}

Microscopic Appearance of Renal Lesions. Microscopically, the lesions in the kidneys correspond with the gross appearance of more or less widespread necrosis of the renal cortex. The variable distribution and extent of these lesions has already been indicated in the preceding paragraphs. The early hemorrhagic lesions described in a few cases are correspondingly hemorrhagic under the microscope, while older lesions, grossly visible as yellow opaque patches, prove to be composed of almost completely bloodless necrotic tissue. Each of these older areas of necrosis is bordered by a hyperemic and hemorrhagic zone corresponding with the red line seen in the gross specimen at the margin of each of the yellow patches.

Within the areas of necrosis the general architecture of the cortical tissue is clearly recognizable, but all component elements are completely necrotic. The glomeruli retain their normal size, as has been confirmed by actual measurements,^{53a} and they appear normally delicate in structure, but the nuclei show marked alterations ranging from pyknosis or fading of nuclear staining to complete disappearance of nuclei. Hirst³³ described in 1 case an increased cellularity of the glomerular tufts, but this appears to be exceptional and the glomerular cell counts made in 11 cases by de Navasquez^{53a} revealed no variations beyond the normal limits. The capillaries usually are described as empty but some authors record the presence of fibrin thrombi,^{6,23,33,44} conglutinated red blood cells,⁶⁵ or fat droplets^{12,65,79} within their lumina. The necrotic tubular epithelium, like the glomerular cells, may show any degree of nuclear degeneration up to complete disappearance of nuclear staining. The cells are swollen, granular and eosinophilic, the cell boundaries are distinct in some cases but in others the cells are merged with one another and their internal borders ragged and indefinite. The lumen of the tubules usually contains granular fragments of desquamated necrotic epithelial cells, hyaline casts and occasionally a few red blood cells or degenerating white blood cells. The nuclei of the interstitial tissue persist for a longer time than the nuclei of the parenchymal cells but in some cases all nuclear staining is lost.

At the margin of the completely necrotic tissue various stages of cell degeneration leading up to necrosis are visible. Fat stains generally reveal some degree of fatty degeneration of the intact tubular epithelium in this marginal zone, while calcification of necrotic epithelial cells near the margin has been described in a few cases.^{26b,41,43} On the other hand, regeneration of the epithelial cells of the peripherally placed necrotic tubules, while apparently not a common event, is described in at least 1 case.^{26b} Glomeruli in this region are usually described as being hyperemic and are frequently distended with blood which may be found also in the capsular spaces. Indeed, there is hyperemia of the whole capillary bed in the marginal zone with minute hemorrhages into the tissue. This hyperemic and hemorrhagic zone tends to be most pronounced along the internal border of the necrotic areas and much less conspicuous or almost lacking in the thin layer of living tissue which separates the areas of necrosis from the capsular surface of the kidney. Except in cases where cortical necrosis is very recent an infiltration of neutrophils is constantly found around the whole periphery of the necrotic tissue, mingling with extravasated red blood cells,

but extending slightly beyond the hemorrhagic zone into the bloodless areas of complete necrosis, where they may be represented only by pyknotic fragmented nuclear remains. There is a notable absence of bacteria in these renal lesions.

In almost every reported case of bilateral cortical necrosis of the kidneys, there is described either some kind of pathologic alteration in the walls of the small arteries in the areas of cortical necrosis, or occlusion of their lumina by some form of thrombosis, or both. The exact state of the arterial walls is not described in every instance in sufficient detail to indicate clearly the character of the vascular changes. A considerable number of authors make no mention of pathologic alterations in the walls of the arteries. On the other hand, in about one-third of the reported cases there is a clear description of definite changes in the arterial walls. These have been especially well described by Geipel,^{26b} Hunt,²⁴ Weaver and von Haam,⁷³ and von Zalka.⁷⁸ The affected arteries are widely dilated, their walls appear swollen and succulent, and the cells composing them are smudgy, or partly disintegrated, being separated from one another by an eosinophilic material in which a network of fibrin threads can be demonstrated by appropriate stains. The internal elastic lamina is frayed and fragmented. The outer layers of the necrotic vessel walls, and the immediately adjacent tissues are infiltrated by disintegrating leukocytes. In other instances the individual cells of the arterial walls are scarcely recognizable as such, since they are merged or fused into a granular or hyaline eosinophilic mass containing an abundant proportion of fibrin. In any given case the arterial necrosis appears to be of about the same age in all affected vessels.^{53a,67} Such changes in the walls of arteries are interpreted as indicating the occurrence of a primary necrosis in the vessels prior to the beginning of necrosis in the surrounding parenchyma.

This type of necrosis involves especially the intralobular arteries, although it frequently extends into the afferent arterioles and even into the hilus of the glomerular tuft. The restriction of this primary necrosis to arteries of the smallest order of size, 150 μ or less in diameter,^{53a} is very striking indeed. Interlobar ("arcuate") arteries are involved only rarely.^{17,38,56} It is especially worthy of note from the point of view of pathogenesis that the primary arterial necrosis has been clearly described in a number of instances as involving segments of the intralobular arteries proximal to the areas of necrosis in the parenchyma.^{20,26b,32,38,44,58,67,78}

Regardless of whether primary arterial necrosis was present or not, there was found in almost every case some form of plugging of the intralobular arteries and their branches. The exact character of the intravascular masses is a point upon which there is considerable difference of opinion between different investigators. Many authors simply state that the arteries are occluded by thrombi, fibrin thrombi or hyaline thrombi, without describing their appearance in any detail. In a number of instances, however, the thrombi are described as being composed of platelets and a fibrin network enmeshing red and white blood cells,^{11,19,28,38,64} or consisting merely of an eosinophilic homogeneous amorphous mass.^{12,36a,37} In some cases such thrombi are described as appearing compact in their peripheral layers next to the arterial

wall but are more delicate toward the center which may even be patent.^{26b,38,67,78} On the other hand, several authors speak of the plugs merely as masses of packed, conglomerated red blood cells with little or no fibrin formation or platelet deposit, and therefore they question that they are true thrombi.^{2,23,53a,65} The presence of stainable fatty substances mixed with the thrombus material has been recorded in 5 cases.^{12,38,64,65,72}

Whatever may be the character of the intravascular masses described in any given case, their distribution is similar in all cases. They occupy the lumina of almost all of the intralobular arteries throughout the areas of necrosis of the parenchyma and frequently extend into the afferent arterioles of the glomeruli and even into glomerular capillaries. In Herzog's case³² the thrombi not only filled glomerular capillaries but were found also in the efferent arterioles. In a considerable proportion of cases it is specifically stated that segments of the intralobular arteries proximal to the areas of cortical necrosis were also occluded by thrombi. It is only in this location that organization of the thrombi has been observed.^{16,26b,66,67,75,78} The absence of organization of thrombi elsewhere is probably explained by the fact that thrombi lie in the midst of totally necrotic tissue incapable of initiating organization. Thrombosis of intralobular veins has been mentioned in 6 cases.^{17,23,28,36a,46,68}

Thus, while there is disagreement as to the exact character of the vascular lesions in the kidneys in bilateral cortical necrosis, all authors, whether they describe primary arterial necrosis, arterial thrombosis or both, agree as to the localization of these changes in the intralobular arteries and afferent arterioles of the glomeruli, to the virtual exclusion of arteries of larger size.

The cortical tissue outside the areas of necrosis and beyond their hyperemic margins usually appears entirely normal, apart from an occasional obliterated glomerulus such as might be found in any kidney. Dalrymple,¹⁶ Penna de Azevedo and de Castro Teixeira,⁵⁶ and Scriver and Oertel⁶⁵ have described each in 1 case evidence of glomerulonephritis in the intact parenchyma in the form of increased glomerular cellularity, thrombosis of glomerular capillaries, and exudate, crescent formation and adhesions in the capsular spaces. Penna de Azevedo attributed the glomerulonephritis in his patient, who had been bitten by a cobra, to the recognized ability of cobra venom to produce renal lesions of this character. Kellar and Arnott⁴¹ mentioned the presence of pyelonephritis in 1 of their cases. In the case reported by Lloyd⁴⁷ there was found thickening of renal arteriolar walls with narrowing of their lumina, interstitial fibrosis and thickening of Bowman's capsules. While necrosis of the cortex may reach the medulla at the bases of the pyramids, there are only 5 cases in which the medullary tissue was even slightly involved in the process of necrosis.^{32,41,50,65} Generally the medulla shows only moderate hyperemia with scattered minute hemorrhages, a slight degree of cloudy swelling, and the presence of numerous granular or hyaline casts in the collecting tubules and in Henle's loops.

Lesions in Other Organs. No changes in organs other than the kidneys are found constantly in association with bilateral renal cortical necrosis. Since the renal lesions sometimes occur with eclampsia, it is

interesting to note that in only 3 cases have lesions resembling eclamptic necrosis of the liver been described.^{36a,58} Central necrosis of the liver lobules is almost as infrequent.^{3,17,22,23,70,73,78} Scriver and Oertel⁶⁵ described multiple, hemorrhagic ulcerations of the large intestine in 1 of their cases, with hyaline necrosis of the underlying blood-vessels. In French's case,²⁰ there was an associated acute pancreatitis. In 4 cases, there were multiple small infarct-like areas of recent necrosis in the spleen with thrombosis of the neighboring arterioles.^{26b,34,65,69} The adrenal cortex contained minute areas of recent hemorrhagic necrosis in 4 cases.^{19,37,58,73} The brain in 3 cases showed numerous petechial hemorrhages, localized to the pons in 1 case^{36b} and to the pons, mid-brain and basal ganglia in another.⁴⁵ In the third case, there was an associated thrombosis of the small cerebral vessels.⁷³ In Cortese's case,¹² fat droplets were found in the capillaries of the lungs as well as in the glomerular capillaries of the kidneys.

Experimental Production of Bilateral Cortical Necrosis of the Kidneys. Within recent years there has been a renewal of interest in the ability of staphylococcal toxin to produce necrosis of the kidneys. The renal lesions resulting from intravenous injections of the toxin in rabbits and cats have been studied carefully by Rigdon, Joyner and Ricketts,⁶⁰ von Glahn and Weld,⁷¹ Glynn²⁹ and de Navasquez.^{53c} All of these authors describe symmetrical necrosis of the outer part of the renal cortex of a character practically identical with that observed in human beings. The earliest microscopic changes are found almost immediately after the first injection of toxin in the form of dilatation and engorgement of arterioles and glomerular capillaries in segments of the cortex, accompanied by alterations in the mitochondria of the epithelium of adjacent convoluted tubules.²⁹ More and more glomeruli become similarly engorged and finally ruptured, while beginning necrosis of the parenchyma becomes evident at the end of about 12 hours. Necrosis is widespread and complete by the end of 2 to 3 days, and by this time the areas of necrosis have lost their early hemorrhagic character. While glomerular capillary damage and dilatation of arterioles are constantly observed, only de Navasquez^{53c} and von Glahn and Weld⁷¹ have described definite necrosis of the walls of the intralobular arteries and afferent glomerular arterioles. De Navasquez^{53c} states that vascular necrosis is the primary event, leading to ischemic necrosis of the parenchyma through plugging of these vessels and glomerular capillaries by packed conglomerated red blood cells. According to von Glahn and Weld⁷¹ ischemic necrosis is caused by occlusion of intralobular arteries and afferent arterioles by fibrin thrombi, while Glynn²⁹ suggests that ischemia is the result of rupture of glomerular capillaries with disruption of the circulation at this point. In addition to the renal lesions, de Navasquez^{53c} describes multiple necroses of the adrenal cortex which he believes are also of ischemic origin.

Reyna,⁵⁸ by the intravenous administration of lithium carmine daily for 2 to 6 days, was able to produce, in a considerable proportion of the rabbits used, renal lesions which he regarded both in their gross and microscopic appearance as identical with bilateral cortical necrosis of the kidneys in man. The outstanding microscopic feature, apart from the necrosis of the parenchyma, was the occlusion of the afferent

arterioles and capillaries of the glomeruli by fibrin thrombi. The widespread thrombosis of these minute vessels was held responsible for the ischemic necrosis of the cortex. Reyna also found infarct-like areas of ischemic necrosis in the adrenal cortex, and necroses in the liver which he stated were similar to those found in eclampsia.

Byrom,⁹ investigating the morbid effects of vasopressin (pitressin) in rats, found that relatively small doses produced only poorly defined areas of pallor in the kidneys with degenerative changes of tubular epithelium in these areas. However, with large doses repeated daily or twice daily, definite pale anemic infarcts were produced in the renal cortex within 24 hours. The extent of the infarction of the kidney varied in different animals but after very large doses in small animals adjacent infarct-like areas of necrosis became merged to produce an appearance closely resembling that of bilateral cortical necrosis of the kidneys in man. Necrosis of the renal arteries was a constant finding when large doses of vasopressin had been given, the smallest arteries being affected by smaller doses and larger arteries by larger doses. Thrombosis of the necrotic arteries or arterioles did not occur. Similar arterial necrosis was observed in arteries in the wall of the stomach and there were also focal necroses of the liver. Both the necrosis of arteries and arterioles and of the renal and hepatic parenchyma were attributed to intense vasoconstriction.

The fact that symmetrical necrosis of the renal cortex occurs in swine infected with the virus of hog cholera is emphasized by Röhrer,⁶¹ who reviews the veterinary literature on the subject and gives a detailed account of the renal lesions based on his own experimental observations. The lesions may take the form of pale, infarct-like areas of necrosis scattered through the renal cortex, or necrosis may involve almost the whole cortical layer, in either case producing a gross picture identical with that observed in certain human cases of bilateral cortical necrosis of the kidneys. The most widespread necrosis of the renal cortex was observed in swine which had been given large doses of pure virus with a view to immunization. Röhrer attributed the cortical necrosis, whether infarct-like or total, to ischemia caused by a primary hyaline necrosis and thrombosis of the cortical arteries which he found constantly in relation to the areas of necrosis of the parenchyma. In association with small infarct-like lesions, the intralobular arteries and afferent arterioles of the glomeruli were affected while in cases of widespread total necrosis of the cortex primary arterial necrosis extended even into the "arcuate" arteries. Infarct-like areas of ischemic necrosis also were found in the spleen in association with arterial lesions of a character identical with those observed in the kidneys.

It has already been mentioned that dioxane and di-ethylene glycol in sufficient doses can cause in man a form of symmetrical necrosis of the renal cortex, which, however, in the case of di-ethylene glycol poisoning, is preceded by marked hydropic degeneration of the renal tubular epithelium and of the central cells of the liver lobules. The necrosis produced by either of these poisons in human beings is accompanied by necrosis of the small renal arteries.^{24,53a} In various experimental animals the administration of dioxane or di-ethylene glycol causes marked hydropic degeneration of renal epithelium and of the

central liver cells, but the renal lesions are described simply as a severe tubular nephrosis. Vascular changes are lacking and the picture of bilateral cortical necrosis of the kidneys is not reproduced.^{10,24,25,53b} Thus it would appear, at least in the case of poisoning by these chemicals, that the pathologic picture of symmetrical necrosis of the renal cortex does not develop without involvement of the small cortical arteries.

Etiology and Pathogenesis. A previous section of this review dealing with the clinical background upon which bilateral cortical necrosis of the kidneys makes its appearance shows that the disease may occur in males or females of almost any age in association with a great variety of apparently unrelated conditions, the etiologic significance of which is extremely difficult to assess. It is obviously impossible to state that there is any specific etiologic factor which is common to such diverse diseases as eclampsia, diphtheria, scarlet fever, pneumonia, tuberculosis, malaria, dysentery, and poisoning with almond extract or cobra venom. However, the cases of this kind evidently form the basis of the idea which pervades the literature that symmetrical cortical necrosis of the kidneys is due to some "toxic" influence. Some of the methods of producing bilateral cortical necrosis of the kidneys experimentally in animals could also be construed as indicating a toxic etiology. If this idea is correct it is obvious either that various toxic substances are capable of producing the same effect on the kidneys, or else that a specific endogenous toxic substance is produced during the course of a variety of unrelated diseases. There are still other cases in which there was a history of the use of substances that are generally considered to be of a "toxic" nature, such as alcohol and thyroid extract, but these substances even in large or fatal doses do not characteristically produce bilateral cortical necrosis of the kidneys. One is obliged, therefore, to consider the possibility that the association of renal necrosis with absorption of such toxic substances is purely fortuitous and that the true cause remains obscure. It is scarcely necessary to point out that in the great majority of instances, eclampsia, diphtheria, scarlet fever, pneumonia, tuberculosis, malaria and dysentery, are not followed by bilateral cortical necrosis of the kidneys. Nevertheless, since the great majority of cases of renal cortical necrosis occur in association with pregnancy or some serious infectious disease, it is almost impossible to avoid the conclusion that the renal disease is somehow dependent upon the condition which immediately preceded it. This same conclusion applies equally well, however, to certain cases in which conditions not ordinarily considered "toxic" in the clinical sense, such as traumatic shock and dehydration, were followed by renal necrosis. Moreover, there are 3 reported cases in which there was no evidence of antecedent toxemia nor, indeed, of any antecedent disease. Therefore, even if it is granted that toxic substances are capable, under suitable conditions, of causing bilateral cortical necrosis of the kidney, it must also be granted that the disease may occur without any evidence that toxemia has played an etiologic rôle. All of this suggests that there may be a factor of predilection or idiosyncrasy inherent in the individual which determines the course of events when that individual is exposed to the influence of any one of a number of

definite toxic substances or to the influence of unknown and, in some instances, undetected general disturbances of metabolism or vasomotor function.

Discussions of the pathogenesis of bilateral cortical necrosis of the kidneys have brought out a number of different and somewhat conflicting theories; but almost all authors agree that the necrosis of the renal parenchyma is ischemic in origin. This view is supported by the infarct-like appearance of the gross lesions, by the presence of a narrow zone of living tissue just beneath the capsule and by the fact that the zone of necrosis beneath this subcapsular layer always occupies the outer part of the cortex, leaving the inner layer intact except in a very few cases in which necrosis extends as far as the bases of the medullary pyramids. The early lesions observed in a few cases^{41, 53a, 73} illustrate the early hemorrhagic stage of ischemic necrosis of the kidneys.⁴⁰ Microscopically, too, the picture is typical of infarction. Hirst,³³ Jardine and Kennedy,^{36a} Manley and Kliman,⁵⁰ and Weber⁷⁴ have suggested that the necrosis is due to a primary damage to the cells of the renal parenchyma, but this possibility seems to be excluded by the fact that a sharply demarcated zone representing only a part of the thickness of the cortex is involved, and by the fact that, in the areas of necrosis, all component elements of both the parenchyma and the supporting connective tissue alike are rendered necrotic.

Among the great majority of authors who regard the necrosis as ischemic in origin, there is considerable divergence of opinion as to the cause of the ischemia. In reporting the first case of bilateral cortical necrosis of the kidneys in 1886, Juhel-Rénoy³⁹ expressed the opinion that the renal lesions were due to multiple embolism, but the absence in his case, and in practically all of the cases reported since that time, of a source of embolism and of evidence of embolism in other organs, together with the uniformity of distribution of the cortical necrosis throughout both kidneys, has led to the rejection of the idea of embolism by all subsequent writers. The only possible exception is Cortese,¹² who found in his case droplets of fat in glomerular capillaries and suggested that this represented fat embolism which had initiated a process of retrograde thrombosis in the afferent arterioles and intralobular arteries. He also described fatty material mixed with the thrombi in these vessels, an observation which has been recorded also in a few other cases.^{38, 64, 65, 72, 73, 79} However, in clear-cut cases of fat embolism, even when the kidneys are massively involved, the picture of symmetrical necrosis of the renal cortex is not reproduced and, as Oertel⁶⁵ has suggested, it is probable that the fatty accumulations in the thrombi represent condensations of finely divided fat into larger aggregations during thrombus formation, the excess fat originating from the presence of hyperlipemia which is common in pregnancy.

It is obvious that ischemia leading to necrosis of a peripheral layer of cortical tissue of varying thickness must be attributed either to an organic or functional occlusion of great numbers of the minute "end arteries" which supply this zone of the cortex. Moreover, vascular occlusion must become effective almost simultaneously in all parts of the cortex in both kidneys which ultimately become necrotic, for it is a constant observation that the areas of cortical necrosis in any given

case all appear to be of about the same age. The descriptions of the pathologic changes in the cortical blood-vessels summarized in a preceding section of this review, all locate the chief vascular disturbances in or beyond the intralobular arteries. With all of these considerations in view, various authors in discussing the pathogenesis of bilateral cortical necrosis of the kidneys have directed special attention to certain peculiarities of the small arteries and arterioles of the renal cortex.

As demonstrated by Gross³¹ and Morrison,⁵² the renal arteries divide into large branches, the interlobar arteries, which course between the cortex and medulla, and gradually decrease in size through repeated divisions. The intralobular arteries, arising everywhere from the smaller divisions of the interlobar arteries, penetrate the cortex in a direction perpendicular to the surface of the kidney, and give off a succession of fine branches, the glomerular arterioles, each of which leads to a single glomerulus. It is to these glomerular arterioles that a specialized function has been assigned by the studies of Richards and Schmidt⁵⁹ on the kidneys of frogs. These investigators were able to show that injection of adrenalin caused arteriolar constriction which was most pronounced in the glomerular arterioles at the point of division into glomerular capillaries. They also observed spontaneous contractility at this point. For these reasons, they thought that the afferent arterioles played a special rôle in the regulation of glomerular bloodflow. By means of a Roentgen ray technique, Milles, Müller and Petersen⁵¹ demonstrated that adrenalin injections in dogs caused a marked constriction of the whole cortical arterial bed, while scarcely any change could be observed in the caliber of larger arteries. The same effect was observed after a short period of chilling of the whole animal, but both epinephrin and chilling failed to produce any discernible effect in kidneys previously denervated. After prolonged chilling, the vasoconstriction observed at first in the intact kidney gave way to marked vasodilatation. De Navasquez^{53a} and others have interpreted such experimental observations as indicating a special susceptibility of the small cortical arteries to various stimuli. In the same connection, Oertel⁶⁵ stated that the whole vascular system in pregnancy as well as in certain infections shows decided disturbances of its general irritability and that such disturbances may affect the vasculature especially of individual organs, leading to long-continued local or general vasoconstriction which may eventually give way to vasoparalysis. He believed that such circulatory breaks may possibly account at least in part for the symptoms of eclampsia referable to the brain, liver and kidneys.

In view of such speculations regarding the importance of hyperirritability of the renal cortical arteries especially under the conditions of pregnancy or infectious diseases, it is important first to determine whether marked and prolonged constriction of these vessels can cause ischemic necrosis of the renal cortex. Penner and Bernheim,⁵⁷ by the daily intrapleural or intraperitoneal administration of massive doses of epinephrin in dogs over periods of from 6 to 30 days, produced in the kidneys hemorrhagic necrosis of individual glomeruli or of small patches of the renal cortical tissue, but the extent of the necrosis scarcely

approximated that of the reported cases of bilateral cortical necrosis of the kidneys. It might be questioned whether the renal necrosis was due to vasoconstriction alone or to vasoconstriction followed by vasoparalysis, especially in view of the hemorrhagic character of the necrotic areas. However, there is less reason to question that vasoconstriction was the cause of the renal necrosis produced by Byrom⁹ in rats by injections of vasopressin, for the areas of renal infarction, the development of which was followed by direct observation in the intact animal, became pale within one-half hour after the first injection and remained pale up to the stage of complete necrosis. These experiments provide strong evidence in support of the view that intense and prolonged vasospasm may be responsible for the development of bilateral cortical necrosis of the kidneys in man. It should be pointed out, however, that proof of the ability of vascular spasm to produce renal cortical necrosis experimentally does not prove that this mechanism is necessarily the one responsible for the renal necrosis in all, or indeed in any, of the cases of the disease in human beings.

The idea that spasm of the cortical arteries is responsible for symmetrical necrosis of the renal cortex has been put forward chiefly by those authors such as Immink³⁵ and Furtwängler²¹ in whose cases no thrombi were found in the renal cortical vessels. In 1 case reported by Jardine and Teacher³⁷ there were symptoms suggestive of Raynaud's disease and Teacher thought, for this reason, that vascular spasm of the smaller renal arteries led to thrombosis of these vessels and consequent anemic infarction of the cortex. However, in a later paper by Jardine and Kennedy,^{36a} the latter, who carried out the histologic studies, stated that he could not support this opinion. Nevertheless, this same idea of vasospasm as the cause of thrombosis was subsequently restated by Cruickshank.¹⁵ Zanzig⁷⁹ believed that vasospasm was the initial event leading in turn to necrosis of the cortical arteries, thrombosis of these vessels and consequent ischemic necrosis of the renal cortex.

Oertel⁶⁵ also thought that bilateral cortical necrosis of the kidneys was dependent upon ischemia produced by vasomotor disturbances, but he constructed a rather complicated explanation based chiefly upon the studies of Ricker and his students. Ash² and Stening⁶⁶ have subscribed in the main to Oertel's theory of pathogenesis and Ash referred to the disease as "angioneurotic anuria." According to Oertel, the various pictures in the kidney represent "the results of irritations of the terminal arterial segments of different intensities," weak irritation causing vasodilatation with increased bloodflow, medium irritation causing vasoconstriction with slowing of the blood current, and strong irritation causing vasoparalysis with dilatation of arterioles and capillaries and slowing of the stream while the proximal arteries remain still constricted. The ultimate result is blood stasis in the terminal arterial segments with conglutination of red blood cells. If circulation is re-established and stasis relieved, corpuscular conglutination is dissolved and offers no obstruction to renewed bloodflow. It is suggested that restoration of circulation in this way may account for recovery in certain cases. While alterations in the blood are regarded as being of importance in the causation of arterial thrombosis, "the actual deciding

event or moment for thrombosis occurs when circulatory irregularity and disproportions through vasoparalysis of terminal segmentary arterial levels supervene." This explanation altogether seems somewhat forced and it fails to offer any reason whatever for the primary arterial necrosis observed in a considerable number of cases.

On the other hand, de Navasquez concluded from the study of 12 cases of bilateral cortical necrosis of the kidneys^{53a} and from the study of the renal necrosis produced experimentally by staphylococcus toxin^{53c} that the primary change in the human cases and in experimental animals is a diffuse necrosis of the walls of the peripheral intralobular arteries of the renal cortex and of their terminal branches unaccompanied by thrombosis. The vascular necrosis is caused by circulating agents of a "toxic" nature to the actions of which these vessels are especially susceptible because of their high functional specialization. The dilatation of the paralyzed and necrotic blood-vessels increases glomerular capillary pressure thus allowing excessive glomerular filtration. The resulting concentration of red corpuscles leads to stasis in glomerular capillaries and the small cortical arteries, with consequent ischemic necrosis of the parenchyma. De Navasquez believed that there is no true thrombus formation in these vessels but merely a conglutination of blood cells without fibrin formation or organization. This theory of pathogenesis is in direct conflict with the observations of those who describe true thrombosis of the cortical arteries or arterioles occurring in either necrotic or non-necrotic vessels with or without organization of the proximal portions of the thrombi.

With the single exception of de Navasquez,^{53a,c} all of the authors who have described necrosis of the small renal cortical arteries have also described thrombosis of these vessels and have attributed the necrosis of the renal cortex to ischemia caused by this thrombotic occlusion. The majority of these writers regarded the arterial necrosis as the primary event and considered it the cause of the thrombosis. French,²⁰ zu Jeddloh,³⁸ Reyna,⁵⁸ Stoeckenius,⁶⁷ von Zalka⁷⁸ and others have attributed the primary arterial necrosis to the direct action of an unknown toxic substance on the vessel walls. Lanza⁴⁴ thought that in his syphilitic patient, who had been given a therapeutic malarial infection, the arterial necrosis was best explained on the basis of an allergic-hyperergic reaction caused by the release of spirochetal proteins. It appears that Zanzig⁷⁹ is the only writer who has suggested that the primary arterial necrosis is due entirely to vascular spasm, although this same suggestion was made by Byrom⁹ to explain his experimental results.

A considerable number of authors have attributed the necrosis of the renal cortex to ischemia caused by thrombosis of the small cortical arteries which they observed in their cases in the absence of any conspicuous pathologic alterations in the walls of these vessels. Several different explanations to account for the arterial thrombosis have been advanced by the different writers in this group. Bradford and Lawrence,⁷ Carson,¹¹ Dalrymple,¹⁶ Evans and Gilbert,¹⁹ Glynn and Briggs,²⁸ Kellar and Arnott,⁴¹ and Stening⁶⁶ have suggested that some form of toxic damage to the endothelium of the cortical arteries is of first importance in the causation of thrombosis of these vessels. Various

changes in the general state of the blood, such as increased coagulability or an increased tendency to agglutination of cellular elements, have been suggested as important factors in the genesis of thrombosis by Bamforth,³ Griffith and Herringham,³⁰ Klotz,⁴³ Rolleston,⁶² Gáspár,²³ Oertel⁶⁵ and Stening,⁶⁶ but the three last named considered that alterations in the blood constituted merely a contributing factor. Teacher³⁷ and Cruickshank¹⁵ regarded thrombosis as secondary to arterial spasm.

The ischemic necroses observed by different investigators in the adrenal cortex, spleen and gastro-intestinal tract, both in man and in experimental animals, have been explained in all instances on the basis of the theory adopted by the respective authors to account for the development of bilateral cortical necrosis of the kidneys.

The foregoing survey of the theories which have been advanced regarding the etiology and pathogenesis of bilateral cortical necrosis of the kidneys shows clearly a lack of general agreement on almost every important point. Diversity of opinion seems to derive largely from the fact that histologic changes differing in important details, especially as regards the vascular lesions in the renal cortex, have been described in different cases by the respective observers, including the most competent, and it is only natural that each investigator should construct a scheme of etiology and pathogenesis that will accord at least with the facts in his own case, marshallng from the literature the evidence to support his theory, but perhaps criticizing or simply ignoring the ideas of others who have developed their arguments on different premises. In spite of all this, there has emerged an almost complete agreement, at least within more recent years, on one point, namely, that symmetrical necrosis of the renal cortex is the result of ischemia caused by obstruction of the circulation through the terminal cortical arteries and arterioles, and all of the facts strongly support this conclusion. However, the etiology of the disease remains a matter of opinion or conjecture, while the succession of events which lead to ischemia of the renal cortex is a question still in hot dispute.

It seems clear that the fundamental and primary disturbance must take place in the terminal arteries and arterioles of the cortex of the kidney. Not only is this indicated by the constant location of the cortical necrosis in the peripheral layers of the cortex but by the fact that the vascular lesions of whatever kind are localized with precision in these vessels. The Reviewers are prepared to believe that the lesions in the cortical arteries are really as varied in different cases as the various descriptions of these lesions would indicate. Indeed, one can scarcely escape this conclusion after perusal of a series of different descriptions. However, in spite of the variations in the vascular changes, the general character of the cortical necrosis is virtually the same in every instance. This can only lead to the conclusion, which seems self-evident, that any mechanism capable of causing more or less simultaneous and prolonged interruption of bloodflow through a large number of the cortical arteries will produce the picture of symmetrical necrosis of the renal cortex. While the actual mechanism of occlusion, as it expresses itself in the final histologic picture in the cortical arteries and arterioles, appears clearly to be somewhat variable, it seems reason-

able to suppose that certain factors in the etiology and pathogenesis of the vascular lesions are common to all cases.

The etiologic agent is unknown, although it has been thought of as a circulating "toxic" substance or "irritant." But it is not known whether this hypothetical agent is the same in every instance, whether it is exogenous or endogenous, or whether it acts directly on the arterial walls or by way of intense nervous stimulation. In any event, it seems clear that the deleterious factor or factors have in common the property of causing, under suitable conditions, disturbances in the terminal arteries of the renal cortex. How serious these disturbances may be, or whether they will occur at all, appears to depend, not only on the properties of the precipitating deleterious factors, but also on the sensitivity of the renal cortical arteries to stimulation or irritation. Experimental evidence has been cited to show that the intralobular arteries and glomerular arterioles normally are especially sensitive to stimulation, and it appears probable that in certain apparently normal individuals these vessels may be abnormally sensitive, or that they may become hypersensitive in certain individuals under the conditions of pregnancy or during the course of infectious diseases. This individual hypersensitivity or hyperirritability of the renal cortical arteries would correspond with the factor of individual predilection or idiosyncrasy suggested in the opening paragraph of this discussion.

It appears entirely reasonable to us to suppose that the actual effects produced in the renal cortical arteries could vary with the degree of hypersensitivity of these vessels, and with the intensity or duration of action upon them of the irritating deleterious factor. Thus, one could conceive of a series of vascular disturbances of increasing severity: intense vasospasm; vasoparalysis; partial or complete necrosis of the arterial walls which might be due either to vascular spasm of extreme intensity or to the direct action of some toxic substance. At any stage in this ascending scale, bloodflow might be halted, either by the occurrence of true thrombosis, or through blood stasis and coagulation of red blood cells in dilated vessels following vasoparalysis, or even by intense vasoconstriction alone. Such a general theory of the etiology and pathogenesis of bilateral cortical necrosis of the kidneys commends itself especially because it brings into accord all of the observed facts, both clinical and pathologic, including the variable alterations observed by different investigators in the renal cortical arteries.

So far as thrombosis of the arteries of the renal cortex is concerned, it seems obvious that general alterations in the state of the blood of such a character as to promote thrombosis must be of importance in those cases where such changes in the blood are known or can be shown to exist. But general alterations in the blood cannot alone be held responsible for thrombosis restricted so sharply to the terminal arteries of the renal cortex and not occurring with any constancy in any other part of the body. It is apparent that the determining factor must be in the renal cortical arteries themselves.

The hypersensitivity of the arteries and arterioles of the renal cortex is apparently shared in certain cases, though in much lesser degree, by the small arteries and arterioles of other organs such as the adrenal, spleen, intestine and brain. Reactions in these vessels similar to those

which occur in the renal cortical arteries could equally well account for the ischemic necroses observed on occasion in these organs.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY.

UNDER THE CHARGE OF

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FAMILIAL SUSCEPTIBILITY TO LEPROSY.

"EPIDEMIOLOGY," as Frost has said, "is something more than the total of its established facts. It includes their orderly arrangement into chains of inference which extend more or less beyond the bounds of direct observation. But it is not easy when divergent theories are presented to distinguish immediately between those which are sound and those which are merely plausible." This has been especially true when epidemiologic inferences have led into fields not yet well bounded or cultivated. Therefore, it is constructive to turn back to the data from which earlier concepts have been evolved in order to retest them in the light of present knowledge. Thus, erroneously drawn propositions may be amended, or the validities in conflicting hypotheses which have been formed from the same observation may be proved adjustable into a different concept.

The evolution which has taken place in the concept of the epidemiology of leprosy can be retraced as far back as biblical times, because it has been more greatly feared than any other disease and hence more closely observed and recorded. Whatever actual evidence may have underlain the ancient theory of contagiousness has been lost in antiquity, but belief in its transmissibility is well shown by the measures taken against the spread of the disease in the time of Moses, as set forth explicitly in the Book of Leviticus. The leper was directed to bare his head, to put a covering on his upper lip, and to cry, "Unclean, unclean!" He was to dwell alone, without the camp. His garments, "if the plague be reddish or greenish" in them, and found to spread, were to be burnt in the fire. The house in which there was leprosy was to be emptied; and if the priest on entering beheld the plague "in the walls of the house with hollow strakes, greenish or reddish, which in sight are lower than the wall . . . then the priest shall shut up the house seven days. And the priest shall come again the seventh day . . . and if the plague be spread in the walls of the house, then shall the priest command that they take away the stones in which the plague is, and they shall cast them into an unclean place without the

city; and he shall cause the house to be scraped within round about, and they shall pour out the dust that they scrape off without the city into an unclean place."

In the Middle Ages, according to the ritual of Paris, the following rules were given lepers by the priest:¹⁵

They were forbidden to enter the church, or the market place, or the mill, or the public fair, or in any company or assembly of people whatsoever (person-to-person contact).

They were forbidden to wash their hands and all necessary things in fountain or in brook or in any water whatsoever, and if they wished to drink were ordered to take water with their own jug or some other vessel (water-borne infection and the drinking cup).

They were not allowed to touch anything that they wished to buy in any place whatsoever, but had to point to it with rod or staff.

While going through the fields, they were not allowed to reply to anyone who might question them except first, for fear they might infect someone, they step off the road to leeward, and also they were not allowed to travel by highway at all for fear of meeting someone (air-borne infection).

If necessity required that they take a path through the field, they were forbidden to touch the hedges, or bush, on either side, except before this they put on their gloves (contamination of objects).

They were forbidden to touch little children or any young people whatsoever and to eat and drink with companions save they were lepers (isolation).

It would be difficult to determine to what extent the foregoing drastic precautionary measures were based on any acceptable evidence of contagion and how much purely upon fear of the "loathsome" disease. In any case, this concept must be classed as an epidemiologic inference, since it long antedated knowledge of infectious agents. But how close the older notion approached our modern concept of contagion is remarkable and is well illustrated by the meticulous measures outlined for the prevention of the disease, measures which might have been set forth by a trained sanitarian of the present day.

The age-old theory of contagion was brushed aside in 1848 by Danielssen and Boeck, who advanced the doctrine that leprosy was almost exclusively hereditary in origin. This theory of hereditary transmission of the disease itself prevailed until the discovery of the infectious agent by Hansen, in 1873. Then contagion once more came to the forefront, in line with the trend in the concept of infectious diseases in general, coincident with the development of the science of bacteriology. Emphasis was turned toward the circumstance of exposure to the infectious agent as the more important determinant in the occurrence of disease, and the mode of spread became the central idea in epidemiology. The discovery of the Hansen bacillus afforded such plausibility to the theory of contagion that after a few controversial years the concept of hereditary transmission seems to have been overwhelmed. To quote Rogers and Muir:²³ "This threw a flood of light on the etiology of leprosy and revolutionized our entire conception of its epidemiology by displacing the then dominant and paralyzing hereditary theory of its origin by the now generally accepted and more hopeful infective one."

The theory of contagion has remained predominant, and the failure of the disease to follow ordinary lines of contagion has been attributed to supposed variations in the degree or duration of exposure to the infectious agent. But with the recognition of the tendency of leprosy to remain restricted to certain regions, races and families for long periods of time—beyond anything which could be explained by corresponding restrictions in exposure—doubt has been thrown upon the belief that contagion is the major determinant in the distribution of the disease, and the place of more remote influences is again being considered.

Thus, there are in the epidemiology of leprosy two divergent theories which have been advanced to explain the transmission of the disease, namely contagion and heredity. These concepts were derived at different times, not so much from conflicting observations as from resisting inferences evolved from essentially similar observations. They were formed long in advance of developments in the specific fields of science involved, and with acquisition of knowledge, discrepancies in each and validities in both become apparent.

The approval of either concept necessitates the acceptance of assumptions of doubtful worth in the theory favored and the rejection of valid evidence in the opposition. There is no question but that the disease is spread through contagion, but the striking tendency to familial occurrence would make it appear that the result of exposure is determined in large measure by an hereditary influence. Webster has demonstrated that inborn susceptibility is a major factor in the outcome of exposure to certain experimental infections. Studies in poliomyelitis suggest that familial susceptibility plays an important rôle in the limited and selective occurrence of the paralytic disease.¹ Still another example might be mentioned where inherited susceptibility has been thought to play a distinct rôle in the manifestations of a disease. It is well known that a comparatively small percentage of cases of syphilis develop general paresis. One explanation for this has been the theory that only certain individuals are susceptible to involvement of the central nervous system with this infection, and that this susceptibility is inherited. This idea has been considered entirely plausible by many students of the disease. A similar concept of the epidemiology of leprosy would harmonize the acceptable features and adjust the discrepancies in the two opposed theories, namely that the disease itself is transmitted hereditarily, and that it results solely from prolonged or intimate contact.

Hereditary Susceptibility. A dual etiology in leprosy, including the factors of hereditary susceptibility and contagion, is by no means a new epidemiologic notion. It was held for centuries in China and was believed in by Virchow, by Liveing and by Solano in Colombia. It was foreshadowed by writers of the early nineteenth century, who included remote circumstances to explain the vagaries in the occurrence of infectious diseases. Thus Gallup²¹ wrote of certain epidemic infections in 1815, "If diseases of this class are propagated by a contagious principle, it is of a singular sort, not subject to the laws of any known contagion," and he "assigned their origin . . . more to remote influences affecting the system which increase liability to disease." Hereditary predisposition to leprosy was emphasized a century ago by Sir James Simpson²⁴ in his statement that, "Few facts in the history of tubercular leprosy

seem to be more universally admitted by all writers on the disease, both ancient and modern, than the transmission of the predisposition of it from parents to offspring." From the literature on the disease in the 1880's, one gathers that many students of the subject held this view. To quote one observer:²⁵ "The disease does not appear to me to be hereditary, that is, transmitted *de toutes pièces* from parents to offspring by procreation, or stored in the blood of individuals for generations in its morbid nature and potential energy, without show of its presence. I doubt not, however, that the greater or lesser susceptibility to contract or acquire the distemper forms part of constitutional inheritance. Families may have received from parents and ancestors inorganic peculiarities, which render their members, or some, or many of them, not necessarily, but eventually, easier preys to the disease, when the exciting cause is brought, with effective force, to act upon them."

Hirsch,¹⁶ who was a proponent of hereditary predisposition, remarked in his criticism of the theory of contagion, "Dr. Hansen forgets that there is such a thing as a congenital morbid diathesis, in which there can be no question of infection, a disposition towards a definite kind of sickness, residing in the organization of the individual by inheritance." He goes on to suggest: "The best ground on which to try this question is obviously afforded by the small, closely circumscribed, and therefore easily surveyed leprosy spots, with a fixed population subject to no changes, where the state of health in the several families may be learned with the least possible trouble and followed through a long series of generations. Areas of observation of that kind existed at the beginning of the century at various points on the coast of Provence, France . . . in several of the coastal districts of Sweden . . . and we will meet with them in southern Russia and the Caucasus . . . and in New Brunswick. . . . For all of these places do we in fact find, in the authorities quoted, classical proofs that the disease clings to particular families as a consequence of continuous inheritance from generation to generation."

Aside from the bacteriologic evidence, there is an abundance of epidemiologic proof that leprosy is an infectious disease. However, the factor of contagion alone is inadequate, since relatively few of those who are exposed develop the disease. The gaps have been filled in by supposed variations in degree or duration of exposure and by "predisposing causes." The following statement by Rogers and Muir²³ epitomizes the modern idea of contagion: "When a case has been established beyond all doubt as one of leprosy, only half the diagnosis has been made. It is no less necessary to find out what is the predisposing cause. We consider that it is firmly established that in an endemic area less than half of those who are inoculated with the germs of leprosy develop the disease. Man, like the lower animals, when in normal health and living under favorable conditions is able to resist the onset of leprosy. Anything which lowers the resistance must be distinguished from natural immunity, although the latter forms a part of the former."

Elsewhere Muir²² states: "Much of the confusion which exists in regard to leprosy is due to want of recognition of the important rôle played by predisposing causes. There is probably no disease in which predisposing causes play a more important part than in leprosy. Many facts might be quoted to prove that, although the bacilli may be present

in the body, some predisposing cause or other is necessary before they can begin to increase in number and produce signs." He then cites a large number of contributory conditions, such as puberty, pregnancy, malaria, syphilis,* chronic bowel disorders, hookworm, unsuitable diet, climate, humidity, lack of exercise, the climacteric, and even laziness, which were regarded as predisposing factors. It is curious that hereditary susceptibility was not included in this sweeping list. It can only be supposed that it did not find a place because the factor of heredity in leprosy was completely set aside with the discovery of the Hansen bacillus, at an epoch when the whole tide of medical thought was turned away from constitution and toward contagion.

Another obstacle to the acceptance of contagion *per se* is the relative infrequency of *conjugal leprosy*. Gwyther recorded that of 178 wives living with leprous husbands 3 to 27 years, only 4 contracted the disease. McCoy and Goodhue give figures of 4.8% for females and 5.1% for males, and Kitasato found only 3.8% of conjugal infections. As a matter of fact, all the figures indicate that husbands and wives do not contract the disease any more often than do unrelated persons (servants, and so forth) living in the household. Hayd¹³ reports an instance of a healthy husband who buried 3 leprous wives while he himself remained strong and well. The relative infrequency of conjugal leprosy as compared with familial occurrence usually has been explained on the basis of decreased susceptibility of persons of marriageable age. However, the age distribution of leprosy, even when set back for incubation period and lapse in diagnosis, does not indicate a decrease in susceptibility with age sufficient to account for the low incidence of conjugal leprosy.

Turning to the concept of hereditary transmission, it is not surprising that the striking occurrence of leprosy in familial lines suggested the hereditary transmission of the disease itself, when it is remembered that the work of Danielssen and Boeck antedated that of Mendel by about 20 years and the recognition of Mendelian heredity by 50 years. Landré, as early as 1869, objected that the alleged hereditary influence showed itself more strongly in the collateral than in the direct line, in his opinion quite contrary to the laws of inheritance, evidently confusing heredity and congenital transmission. Similarly, Muir omitted cases in collateral relatives as affording no evidence of hereditary influence. Holmsen recorded 93 lepers, 12 (13%) of whom had parents or grandparents who suffered from the disease. As an argument against heredity, he points out that in no less than 11 of the 12, the parents or grandparents were attacked after the birth of the children.

J. C. White, in 1882, pointed out that such evidence as had been brought forward in support of the hereditary origin of leprosy was based on inquiries in restricted geographic regions where leprosy has prevailed for centuries among certain classes, and in small districts where affected families have intermarried for generations and where the continued appearance of leprosy in the descendants of such families "may be as good evidence of its communicability as of its hereditary origin," and he contended that the theory of heredity will not hold good in any instance without the absolute demonstration that inoculation

* "Leprosy is the fourth stage of syphilis, a stage that white men are exempt from in the majority of cases . . . by reason of hereditary immunity."

has been impossible. Rogers and Muir state: "It may be observed that nearly all recorded data in favor of the hereditary origin of leprosy belonged to a period when the leprosy bacillus was either unknown or not fully established. It may safely be said that all of the evidence is now in agreement with the statement of Munro in 1879 that no proof can be brought forward that leprosy has the true character of a hereditary disease in being transmitted whether the children live with the parents or not." Manifestly, such criticisms as these are directed against hereditary transmission of the disease itself and as such are valid. The data which Danielssen and Boeck presented to substantiate their belief in the hereditary transmission of leprosy reveal the tendency of the contagion to restriction in high degree to family lines.

Mauritz reported infection in Hawaii of 9 out of 17 children 3 to 14 years of age. Denny's extensive statistics in the Philippines showed 16 % of infections among children 1 to 10 years old, and as many as 44 % in those who had lived with leper parents for from 7 to 10 years. Figures from the Culion leper colony up to February, 1922, showed infection of 308 (14.2 %) children born there and not separated from their leper parents, while 18.8 % more showed suspicious signs of the disease, bringing the total of probable infections to no less than 33 %. Sand and Lie reported that of 2010 children of 587 couples, 7 % showed infection when the father alone was a leper, 14 % when only the mother was diseased, and 26 % when both parents were lepers. In Japan, Kitasato found 7 % of the children of lepers contracted the disease.

Hansen, in spite of being aligned on the side of the contagionists, recorded 51 out of 210 patients who had leper relatives in the direct line of ascent. Vandyke Carter reported that in the Kattiawar State in the west of India, relationships between lepers showed some direct or collateral taint in 30 %. Ehlers, of Copenhagen, recorded that in 1897 he found in Iceland 56 of 119 patients who had leper relatives: one or both parents in 22, brothers and sisters in 20, and grandparents in 14.

Brinckerhoff⁶ reported 84 out of 460 cases which gave some family history of the disease: father or mother, 36 cases; brother or sister, 24 cases; cousin, uncle, aunt, and so forth, 18 cases; father and mother, 6 cases; son or daughter, 2 cases. He felt that these data only partially portrayed the familial occurrence of the disease . . . "for it is exceedingly improbable that the patients, whatever their suspicions might be, would reveal the source of their infection. This reticence is broken only when a member or members of the family are already subjects of segregation." One cause for this secretiveness is the widespread belief among the Hawaiians that leprosy is a disease transmitted by sexual intercourse.

McCoy¹⁹ collected over a period of 13 years statistics of 461 cases in which there had been known association with a leper; in 316 of these the contact had been with a member of the family. Illustrative of many records in the literature that are indicative of a familial tendency is the report of Thin²⁶ of the lineal occurrence of leprosy in five generations. No record is given of the disease in collateral lines.

To determine to what extent leprosy was propagating in families in Louisiana, Hopkins and Denney¹⁷ selected for study the first 100 cases at the National Leprosarium in which complete family histories were obtained, and added all subsequent information concerning the appear-

ance of leprosy in other members of these families during the 15 years that had elapsed since the admission of the last of these patients. These original patients were members of 100 families consisting of 100 fathers, 100 mothers and 474 brothers and sisters, a total of 674 persons in the immediate families, which therefore averaged 6.7 persons per family. Of this group of original cases, 64 represented instances of only 1 leper in the family without further known propagation of the disease. In the families of the other 36 lepers, however, there developed 83 additional cases, and this group of 119 lepers presents interesting evidence of familial tendency. There were 5 instances in which the disease occurred in a father and 1 or more of his children, 15 instances in sons of lepers, 21 instances in daughters of lepers, 38 instances among brothers, and 31 instances among sisters. In addition, the following number of cases occurred in less closely related members of the family: 8 uncles, 8 aunts, 18 nephews, 9 nieces, 5 granddaughters. Furthermore, Hopkins and Denney stated that among all the patients admitted to the Louisiana Home (which at that time, 1929, received only exceptionally patients outside the state) an astonishingly large percentage was found to be closely related by blood. As many as 33 % were parent and child, brother and sister, uncle or aunt, nephew or niece. In one instance reported, a woman who was a conjugal leper was herself a member of a leprous line: her father, mother, 4 brothers, 1 sister and a nephew developed the disease.

It would thus appear that the definite tendency which leprosy shows to restricted occurrence in family lines and its failure to spread to persons who, though closely associated, are not related by blood ties can best be accounted for by familial susceptibility. This conclusion leads to the consideration of a new concept to explain the transmission of the disease: admitting the necessity of exposure, and casting hereditary susceptibility as the predisponent necessary in the development of the disease.

Dual Etiology. In a disease which is determined by both contagion and some selective predisposition, such as hereditary susceptibility, the distribution of cases would tend to resemble that of contagious diseases where the proportion of susceptibles in the population is high; and only where there is little suitable material would restriction to certain categories of individuals become apparent. Thus, the theory of contagion as the sole etiologic factor in leprosy doubtless has received its strongest support in areas where the proportion of susceptibles has been high. On the other hand, in regions in which this factor has been restricted, as in Norway, the features presented might well have accounted for the hereditary theory.

A dual causation would adjust many of the factors in the existing theories which are at variance with our definitive knowledge of the respective means of spread. It may explain, for example, why leprosy possesses a high degree of communicability for those connected by blood ties, and is well-nigh non-communicable for unrelated individuals living in equally close proximity to cases, such as nurses and attendants, husbands and wives. It might reconcile a discrepancy in the theory that the disease itself is hereditary, namely, that sometimes a parent may not develop the disease until after the birth of offspring who later become leprous. The proposed concept might also make clear the

reason why the disease spreads extensively when first introduced into a given population (Nauru), on the grounds that a large number of susceptibles have accumulated over an interval when the group was not exposed to infection, as well as why the disease remains restricted to small foci for long periods of time. In short, a twofold etiology would reconcile the paradox of the low contagiousness in general of a disease which under certain circumstances is highly communicable.

It would hardly be expected that members of certain family lines would be confined to very sharply localized areas, or that the infectious agent itself could by any conceivable chance be so restricted. Sharply localized foci of a disease might well exist, though each of the two factors is less limited since there is a diminished chance of the two spreading in the same direction. The outer boundary of a disease resulting from either contagion or heredity would be far more extensive than that of a disease resulting from the coincidence of the two in the same individual.

The results from human inoculations are in keeping with the concept of dual causation. Danielssen, Profeta, Cagnina and Bargilli failed to infect themselves, but in Arning's well-known case of the convict Keanu the disease did develop after inoculation. Although this case is somewhat spoiled as an experiment by the fact that the man had lepers among his relatives with whom he was in contact before and after inoculation, there would seem to be little question from the fact that he experienced pain in the inoculated arm in 1 month and a nodule appeared $4\frac{1}{2}$ months later at the site of inoculation, that the disease in this instance might well have developed from the inoculation, due to the fact that the inoculated individual possessed an inherited susceptibility to the infection.

Belief in a dual etiology in leprosy has been expressed many times by students of the disease, but no specific studies seem to have been made to verify such a conception. Since the establishment of the infectious nature of the disease, much of the data available in regard to familial occurrence has been incidental to efforts to trace the sources of contagion, which in a high percentage of cases have been blood relatives. In order to test the concept of hereditary predisposition, an exhaustive study should be made of the disease in family lines, specifically: 1, to evaluate the significance of the frequency with which the infection is communicated to relatives in comparison with others who are in similar close proximity to cases; 2, to ascertain whether conjugal infections, when they occur, are not largely restricted to individuals who are themselves members of leprosy lines; 3, to investigate epidemiologically a third group, those cases who are members of leprosy families, but who contracted their infection from sources other than members of their own families.

The obvious and permanent manifestations of leprosy, as well as the fact that a large proportion of cases have been recorded and put under institutional observation, remove the large error resulting from missed, forgotten or unknown cases which would be encountered in diseases which run a rather temporary course. The disease on the American continent, because of its low incidence and restriction to sharply localized foci, presents particular advantages for epidemiologic studies of the sort proposed. Leprosy persists among the Acadian French in New

Brunswick, Canada, and in Louisiana; in Galveston, Texas, predominantly in those of German blood; until recently in a small focus among the Norwegians in Minnesota; and in Key West, Florida. It is endemic in Corrientes in Argentina and in Paraguay, and it is an important public health problem in Brazil and Colombia today.

The elucidation of the phenomenon of hereditary predisposition to leprosy, which would appear to constitute a necessary adjunct to the completion of the cycle of infection, might serve to bring into sharper focus the actual mode of transmission by redirecting the search, hitherto fixed on peculiarities of exposure in those infected, to study of undifferentiated and perchance simpler circumstances of exposure shared by both susceptible and insusceptible persons. The accomplishment of this objective might lead to more effective and immediate measures for the control of contagion. Coincidentally, an understanding of the Mendelian behavior of susceptibility might create a consciousness of the biologic importance of heredity, and this knowledge might be expected in turn to exert, through the eugenic control of autarceologic susceptibility, a deterrent effect on the leprosy of the future.

Regional, Racial and Familial Selectivity. Leprosy, not indigenous to North America, has been introduced into all sections of the continent but has not spread except in a few sharply circumscribed areas. One feature of the disease in each of these foci is its tendency to remain restricted through successive generations to certain racial stocks, immigrant from regions of prevalence or in whom the disease occurs elsewhere. Other nationalities within the areas are nearly or entirely exempt. Furthermore, these foci tend to be sharply delimited by the boundaries of the areas populated by the particular groups concerned. The localities involved are widely separated geographically, and differ markedly with respect to environmental influences. Although various nationalities are represented in the several foci, in the two which are the largest and most widely separated, the affected individuals are of a common ancestry.

These observations suggest that the continued occurrence of leprosy in certain localities on this continent is not dependent on the presence of infected individuals alone, or on environmental factors peculiar to these areas, but that, in addition to the presence of cases as sources of infection, it is contingent on some circumstance which is inherent in individuals of the groups involved.

Leprosy in Minnesota. Leprosy was introduced into Wisconsin, Iowa and especially Minnesota in the middle of the nineteenth century by some 160 cases among the Scandinavian immigrants to the Northwest. Data on 52 such cases were published in 1900 by Bracken.⁵ The histories of 12 cases were not available, while 18 had developed the disease in Europe and 28 after coming to the United States. The longest interval elapsing between immigration and the occurrence of symptoms was 20 years; in 19 cases the period was under 10 years; and in 9, it was between 10 and 20 years. These intervals are not inconsistent with the belief that the disease was contracted prior to departure from Europe. Of the 52 cases, 35 died before 1900. Little is known of the first 17, but according to Bracken "from various reports it is safe to assume that they were all from Norway." Of the remainder, 30 were from Norway and 5 from Sweden.

Hansen visited Minnesota in 1888 for the purpose of studying the propagation of leprosy among the Norwegian immigrants and their descendants in this new environment. He reported¹² in refutation of the theory of hereditary transmission, "We have demonstrated by our investigations in North America that of the numerous descendants of Norwegian lepers there, not one has developed the disease." This observation was widely quoted in the literature as convincing evidence against heredity as a factor in the epidemiology of leprosy. Rogers and Muir²³ state: "The most striking example of this (the diminution or absence of leprosy where it should have continued if essentially or even largely an hereditary disease) is furnished by Hansen's observations on 170 Norwegians, who migrated to the temperate northern portion of the United States of America, especially Minnesota, when either suffering from leprosy or in the incubation period of the disease; yet at the time of Hansen's visit to America, not one of their descendants up to the third generation had developed leprosy under the favorable hygienic conditions they lived in, which would not have prevented the occurrence of an hereditary disease."

Thirteen years after Hansen's visit (1901), Burnside Foster¹⁰ reported a case of leprosy in Minnesota in an American-born descendant of one of the affected Norwegian families. Referring to Hansen's dictum, Foster said, "You are all familiar with the statement, so frequently made, that all the cases of leprosy in the Northwest have had their origin in some leprous district or some other country, and that for some unexplained reason the disease was never communicated to others here, although there has been abundant opportunity for such communication. This case puts the matter in a new light." Foster's report, correcting the widely accepted conclusion of Hansen, seems to have passed almost unnoticed.

Hansen's observation was not only premature, but was based on insufficient data. Even at the time he was in Minnesota, the patient reported by Foster was already suffering from the disease—he developed symptoms about 1885 and died in 1898, but the case was not reported until his brother was diagnosed as leprous. This was about 14 years after Hansen's visit and 40 years after the immigration of the patient's father from Norway. The patient is said to have had a leprous uncle in Norway whom he had never seen, and in infancy to have been nursed by a woman who had 2 brothers who were leprous. However, since none of his family had had leprosy in America, he was not exposed to "prolonged and intimate contact with members of his own family," to which the familial occurrence of the disease is generally attributed.

Leprosy has continued in Minnesota up to the present time, apparently largely in the descendants of the affected Norwegian families. Indeed, Bracken²⁷ has stated, "We have no record of leprosy occurring outside the family of a leper in Minnesota." A contemporary case is a woman whose grandmother, mother and uncle had the disease. The grandmother was born in Mora, Sweden, where she lived with her foster mother who had leprosy. She came to Minnesota in 1887 and married in 1888. She had 4 children, 2 of whom—the mother and the uncle of the present case—developed the disease.

Leprosy in Manitoba and Saskatchewan. In addition to the cases of leprosy from the New Brunswick focus, 23 patients have been ad-

mitted to the Tracadie leprosarium from other parts of Canada. Of this group, 13 were sporadic, from various parts of the Dominion, most of them known to have resided previously in foreign leprous areas. The remaining 10 were admitted from Manitoba and Saskatchewan, the only two localities outside of New Brunswick which present any degree of concentration of the disease.

Manitoba. Four patients, all of them Icelanders, were admitted to Tracadie from Manitoba in 1897, 3 from Winnipeg and 1 from Selkirk. Case records are not available, but it may be presumed that they brought the disease from Iceland, where it has existed for centuries and where the reported figures reached the high mark of 226 cases in 1896.

Saskatchewan. Six patients having been admitted from the Province of Saskatchewan, 5 Russians and 1 Syrian.

There are in Saskatchewan small colonies of Dukhobors, a Russian religious sect, whose members are opposed to participation in military service and for this reason were a persecuted people in their own land. In 1840-1850 they were banished from the government of Tauris to Transcaucasia, near the Turkish frontier. This region, south of the Caucasus Mountains, between the Black and Caspian Seas and extending into Azerbadjian, Armenia, Turkmenia and the frontier of Iran, is known to be infected with leprosy.

In 1899, about 7500 Dukhobors emigrated to Canada, where the Canadian government allotted them land in the Province of Saskatchewan near Yorktown, Thunder Hill and Prince Albert. They comprise but a minority of the population in Saskatchewan, yet 5 of the 6 cases of leprosy from that province have been in Russians, from villages in the region settled by the Dukhobors; 1 case being from the town of Verigin, named for the Dukhobor leader in Saskatchewan. Professing as they do opposition to form in religion, it is probable that marriage is limited to the members of their own group.

Four of the 5 patients evidently were born years before the colonization of the Dukhobors on this continent, and presumably were infected in their native land. The interval elapsing before their admission to the leprosarium may indicate a relatively long incubation period, but it is not known how far advanced the disease was when it was detected. The date of birth of the fifth patient would suggest that the individual was born in Canada and developed the disease there; and information has been received recently which corroborates this assumption. The nationality of the sixth patient from Saskatchewan is given as Syrian. Since both the places of origin and of settlement of this individual are adjacent to those of the Dukhobors, the speculation is permissible that he may have been of the same group but had lived across the border from the Dukhobors in Russia.

The immigration of the affected groups in Manitoba and Saskatchewan was recent (the Dukhobors in 1899) and the cases, with one exception, presumably were imported. If we take the Minnesota experience as a criterion, it may still be too early to expect to find additional cases in the descendants of the original Dukhobor or Icelandic immigrants. In Minnesota, with a much larger number of immigrant cases, the first occurrence of the disease in an American-born descendant of the affected Norwegian families was reported in 1902, some 40 years

after the arrival of the family in this country and 14 years after Hansen's visit and erroneous conclusion. The single known American-born case in the Saskatchewan group was reported in 1930, 31 years after the Dukhobor immigration. An imaginary study of the cases in this focus, corresponding to Hansen's study in Minnesota in 1888, would have been made in 1927, and the disease would not have been revealed in any Canadian-born descendant of the Dukhobors, since the first case among them was not discovered until 1930.

Leprosy in New Brunswick and Louisiana. An outstanding feature of established leprosy on the North American continent is its continued occurrence in people of a common origin who live in two widely separated and circumscribed areas.

Approximately 300 cases have been recorded from 1815 to the present time in northeast *New Brunswick*, in an area not larger than a county, lying between the mouth of the Miramichi River and the Baie de Chaleur. This territory was partially settled by Norman immigrants, many of whom fled from Nova Scotia at the time of the Acadian expulsion of 1755, crossed the isthmus and scattered along the shores, forming settlements at intervals as far north as the St. Lawrence River. The disease was first detected in one of the older settlements, composed almost entirely of French Acadians of Norman descent.

The first recorded case in New Brunswick was that of a French woman whose paternal grandfather came from St. Malo, Normandy, where leprosy existed. She developed the disease between 1815 and 1818 and died in 1828. Her husband subsequently became leprous, as did also two of her sisters. The disease gradually spread thereafter.

The actual origin of this focus is shrouded in mystery. One account is that the first case was contracted by washing the clothes of sailors who came to Caraquet, New Brunswick, from France. It has also been asserted that, in 1815, two Norwegians took passage in "La Florida," a ship which navigated the Baie de Chaleur. These men, who were in an advanced stage of leprosy, left the vessel at Misonette, opposite Caraquet, and coming to Tracadie spent some days with the family in which the first cases occurred.

The records of leprosy in New Brunswick unfortunately go back only to 1815. At about this time the disease was occurring in some 4 or 5 families who had come to Tracadie together after the Acadian expulsion and were probably already interrelated.¹⁴ From 1844 to the present time, 311 cases have been admitted to the leprosarium in Tracadie, practically all of whom came from a few villages in the east of Northumberland and Gloucester counties, comprising an area bounded by Chaleur Bay, Miramichi Bay and the Bay of Fundy.

An analysis of the records² from the point of view of familial occurrence reveals interesting relationships. The 311 cases bear only 87 different surnames. These figures, however, may be appreciably altered when more closely examined.

1. Eighteen immigrant cases admitted from other parts of Canada may be excluded, leaving 293 cases with 69 surnames.

2. Variations in spelling in branches of some of the older families account for 12 additional designations, bringing the number of family names to 57.

3. The list includes 58 cases whose 18 surnames are foreign to the

community, but who are nevertheless members of the local families, leaving 39 family lines to account for 293 cases.

4. Lack of familial data makes it necessary to omit 25 families with 41 cases. Thus, there remain 14 families in which 252 cases occurred.

5. Furthermore, 128 of the 252 cases actually bear the same surnames as 8 of the cases admitted to the leprosarium in 1844. Inter-marriage between these original families has been extensive up to the present time. An interesting note is that the 4 most recent patients admitted to the leprosarium actually bear the same surnames as cases admitted in 1844.

Leprosy was first recorded in *Louisiana* in 1766-68, during the administration of Ulloa, when cases occurring among the French were isolated at Balize at the mouth of the Mississippi River. In 1785, Miro established a leper hospital at New Orleans, which had but a brief existence. Subsequent sporadic cases attracted little public interest, and it was not until 90 years later (1872) that Joseph Jones¹⁸ noted the increasing importance of the disease in certain parts of Louisiana. The cases which he observed were principally in persons of French descent, many being offspring of the Acadians who were driven out of Nova Scotia in 1755 and recolonized in Louisiana. The occurrence of leprosy in the Acadians both here and in New Brunswick suggests that it may have been carried to Louisiana by these people, but there is no record of the disease among the Acadians in Nova Scotia, their original home on this continent. The record indicates that the disease was introduced into the two areas long after the Acadians had separated and the groups had gone their different ways.

In 1888, Blanc⁴ reported having seen 42 cases in New Orleans in 5 years. Their histories indicated that they were epidemiologically related to the Acadians, to immigrants from the West Indies, or to more recent immigrants from western Europe.

Denney⁸ traced the origin of 471 cases which had developed in Louisiana and found that 391 of the patients were born in the state, 43 came from elsewhere in the United States, and 37 were foreign-born. He concluded from these figures that, "There is in the state of Louisiana some inherent, although undetermined factor which renders its populace more liable to develop the disease." That this factor resides in the people rather than in the environment is suggested by the preponderance of the disease in Louisiana among certain racial stocks, the existence of foci in two widely separated areas each populated by a certain group, and the restriction of the disease to localities occupied by people of the racial stocks involved. The suggestion is that the Louisiana focus, apparently on the wane, took on renewed activity with the introduction of German immigrants, probably including susceptible individuals, since the occurrence of leprosy principally in people of this stock extends into eastern Texas, where there are large German settlements.

The figures of the occurrence of leprosy in Germans of New Orleans is suggestive. Of 370 lepers reported in the United States, 34 are of German blood; and 12 of these were born in New Orleans, 7 being also admitted from there. A total of 27 cases are recorded as born in New Orleans. Thus, not only is the ratio of German lepers born in New Orleans to the total number of cases of German extraction in the United

States far out of proportion to the population distribution, but there is also a lack of correlation between the number of New Orleans born lepers who are German and the population composition of that city.

Because branches of the same families who went to New Brunswick from Nova Scotia are known to have colonized in Louisiana, studies of the familial occurrence of leprosy begun in New Brunswick were extended to the Louisiana focus. At one time within recent years, there were in the leprosarium at Carville 106 patients who were either born or admitted from 45 Louisiana towns, 40 of which were in the Teche country. A survey of telephone directories available showed family names associated with leprosy in New Brunswick in 24 of the 27 towns. The names of the 14 family lines responsible for the majority of cases in New Brunswick were found in 22 towns.

A visit to the Teche country yielded the names of 114 patients, past and present. Satisfactory genealogic information was obtained concerning 60 of these cases: 25 names neither corresponded to those of the New Brunswick patients nor did such names appear in the genealogies; the remaining 35 cases either bear the same names as cases in New Brunswick or have these names in their lines, 25 actually bearing 9 surnames corresponding to those of New Brunswick patients; and 6 of these are among the 14 New Brunswick families which have contributed the largest number of cases in the Canadian focus. Furthermore, 7 of these 9 families in Louisiana are interrelated.

Genealogic records seemingly having been broken off with the expulsion of the Acadians, it was not possible to establish actual consanguinity between cases in New Brunswick and Louisiana. That these people are related, however, is indicated by the fact that they came from the same place and bear the same names; and there may be added the interesting observation made by a group of Acadians from the Maritime Provinces who visited in Louisiana that they "... took pleasure in naming people by their family names when meeting them for the first time, the resemblance to people of the same names in New Brunswick being so striking."

Other Foci. A number of other instances of sharply circumscribed areas of prevalence exist, where there are sufficient recorded data to suggest that the disease conforms to the characteristics found in the foci studied.

Norway: There were, in 1940, 18 patients in the leprosarium in Bergen, Norway.³ They came from scattered localities, not from any one place or single family. Twelve of them give a history of having leprous relatives. While a number of these cases are in siblings or contemporary relatives, where exposure may be presumed, in 4 cases either the connection was very remote or the leprous relative had died before the birth of the contemporary case.

Nauru: Nauru, an island in the south Pacific with a population of 2200 (divided equally between Nauruans and imported labor), had in 1922 a total of 35 lepers, 34 of whom were natives and 1 a Caroline Islander. These cases have been assumed to be due to contact infection. It must be noted, however, that the disease was almost entirely confined to the Nauruans, among whom there is a high degree of consanguinity. Indeed, 10 examples of close kinship were brought out in the 34 cases.²⁰

Australia: Studies of leprosy in Australia,⁷ particularly in the aborigines, afford evidence of similar familial concentration of the disease.

Leprosy in the United States. Certain regional, racial and familial relationships of leprosy throughout the United States, based on an analysis of data (unpublished) concerning 927 admissions to the U. S. Marine Hospital, Carville, La., during the period 1921-39, are in conformity with those in the individual foci.

The 430 foreign-born cases included in the data were probably importations, since they came for the most part from countries where the disease is known to be prevalent. A certain correspondence in geographic distribution exists in some instances between the foreign-born cases and cases originating in this country. On the other hand, however, some states with a considerable number of imported cases have no domestic leprosy. Considered racially, there is still less correspondence. The disease may spread to individuals in the area of the same race that brought it, but just as often is associated with other racial groups living there; or it may not spread at all. In no case does leprosy go through all the racial stocks in the areas involved in proportion to their numbers. Thus, it may be assumed that the introduction of leprosy from without explains only in part the existence of leprosy foci in this country.

The 497 American-born cases in the series were divided for epidemiologic study into two groups: 1, those born and admitted from the same state; and, 2, those born in one state and admitted from another. The geographic distribution of the 396 stationary cases probably presented a more accurate index of distribution because of the difficulty of setting accurately the time of infection in this disease, with its variable and often prolonged incubation period. The allocation of these cases reveals four major foci of the disease—California, Texas, Louisiana and Florida. A number of additional cases were associated with Mississippi, Alabama, Georgia, South Carolina, Minnesota and Wisconsin, states which may be considered lesser foci, since they have been concerned in the occurrence of the disease over a long period of time. The distribution of the 101 migrant cases shows a high degree of association by either birth, admission or history of residence with the same leprosy foci with which the stationary cases are connected.

The factor of contagion is shown by the fact that 491 of the 497 domestic cases can be allocated to known areas of prevalence either here or abroad, leaving only 6 cases which may be taken to represent the strictly sporadic occurrence of the disease within the United States. Two of these cases were questionably sporadic. The remaining 4 were all of German stock—and 2 of them were mother and daughter.

The involvement of a single racial stock in these 4 cases prompted an analysis of cases of German descent in this country. There is a concentration in Texas, coinciding with the area involved in the focus of the disease there. While in Louisiana the main focus of the disease in another racial group is outside New Orleans, the concentration of cases in German stock is almost entirely within this city. The remaining cases of German descent occur in less defined areas in mid-United States. Regional relationships have been established between cases. The proportion of Germans among imported and domestic cases in

this country where the race was known is as follows: of 378 foreign-born cases, 6 (1.58%) were German. Of 249 domestic cases born and admitted from the same state, 33 (13.2%) were German, and of 58 migrant cases, 10 (17.2%) were of this race.

Leprosy in the United States may therefore be said to be predominantly confined to certain sharply defined areas, and furthermore to certain racial groups within these areas. The records now extend over a sufficient period of time to show that within these areas the disease has continued to occur in successive generations in the same family lines.

Thus, studies of leprosy "in small, closely circumscribed, and therefore easily surveyed leprosy spots, with a fixed population subject to no changes, where the state of health in the several families may be learned with the least possible trouble and followed through a long series of generations" (Hirsch¹⁶) reveal serious discrepancies in the two epidemiologic concepts that have at times been dominant: 1, that the disease is transmitted hereditarily; and 2, that it is propagated by contagion. A third concept is indicated, namely, that leprosy is propagated by contagion through active cases of the disease, but that its occurrence in those exposed is secondarily largely influenced by autarceologic susceptibility to the infection, which is an inherited character.

The studies reviewed here, concerning the racial, regional and familial occurrence of leprosy, indicate two particular lines of approach which should bring the factor of hereditary susceptibility into sharper focus: 1, more exhaustive genealogic research in foci of the disease, such as exist in the United States, where the disease is confined largely to certain racial groups; 2, more detailed studies of conjugal leprosy, in order to test out the validity of the idea that the relatively infrequent cases are attributable to the fact that the mate who contracts the disease is a member of a family in which leprosy occurs and is therefore presumably hereditarily susceptible.

W. LLOYD AYCOCK, M.D.

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PHYSIOLOGY.

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF JANUARY 21, 1941.

Some Physiologic Effects of 11-desoxycorticosterone and 17-hydroxy-11-dehydrocorticosterone in the Partially Depancreatized Rat. D. J. INGLE and G. W. THORN (Cox Institute, University of Pennsylvania, and Johns Hopkins Hospital). Partially depancreatized rats, and adrenalectomized, partially depancreatized rats were used to compare the physiologic properties of 11-desoxycorticosterone acetate and 17-hydroxy-11-dehydrocorticosterone. Treatment with 1, 2 or 5 mg. of the latter compound was followed by glycosuria, ketonuria, an increase in the excretion of non-protein nitrogen, potassium and inorganic phosphorus, loss in body weight and ultimately resulted in the death of the animal. However, all of the increased glucose excretion could not be accounted for on the basis of increased glucose formation from protein. Treatment with equivalent quantities of 11-desoxycorticosterone acetate failed to induce glycosuria, ketonuria or increased non-protein nitrogen excretion, but a slight increase in potassium excretion, unaccompanied by an increased excretion of inorganic phosphorus, was noted following its injection. Larger doses of 11-desoxycorticosterone acetate (10 mg. daily) induced glycosuria in 2 of 3 animals so treated. In contrast to the effect of 17-hydroxy-11-dehydrocorticosterone, treatment with 1, 2 or 5 mg. of 11-desoxycorticosterone acetate was followed by a striking decrease in the renal excretion of sodium and chloride in 11 of 12 experiments.

The Response of the Human Uterus to Posterior Pituitary Extract During Pregnancy. D. P. MURPHY (Gynecean Institute, University of Pennsylvania). The uterine contractions of a series of pregnant women were recorded with a Lóránd tocograph. During the recording period some of the patients received intramuscular injections of posterior pituitary extract. Part of the latter group were treated at weekly intervals throughout the greater part of pregnancy with a dose which was constant from week to week.

The observations throw light upon the following questions: *a*, the earliest time in pregnancy at which spontaneous and induced uterine activity can be detected by the method; *b*, the influence of advancing pregnancy upon spontaneous and induced activity, and upon the interval between treatment and response; *c*, the influence of both the parity of the patient, and the degree of tension of her uterine wall upon the nature of the response to posterior pituitary extract; *d*, individual differences in response throughout pregnancy.

The Behavior of Dorothy Reed Cells in Tissue Cultures.* MARGARET REED LEWIS (Carnegie Institution of Washington and The Wistar Institute of Anatomy). In earlier studies† it was found that the cells of blood-forming organs could be identified in tissue cultures by their characteristic mode of locomotion shown by motion pictures. An effort was made to determine the nature of the cells characteristic of Hodgkin's disease by comparing their behavior with that of normal cells and of malignant cells from lymphosarcomata, monocytomata, and myeloblastic sarcomata.

Cultures of the glands of patients with Hodgkin's disease exhibited a luxuriant outgrowth of giant stroma cells containing large single or multilobed granular nuclei with large nucleoli. Tripolar and bipolar mitotic figures with an increased number of chromosomes were present.

Lymphocytes, Dorothy Reed or Sternberg cells, and stellate macrophages grew out in the early cultures and their subcultures, but within a few days they were overgrown by stroma cells.

The small Dorothy Reed cells migrated freely with a writhing motion, some of them being identical in size, shape and locomotion with the myeloblasts. The large Dorothy Reed cells were sluggish, and in size, shape and movement resembled the megalokaryocytes, except that while many of the Dorothy Reed cells were multinucleated, their nuclei were not lobed and had heavier nuclear membranes and larger nucleoli than those of the megalokaryocytes. They were not phagocytic and did not move like normal macrophages, epithelioid cells, or Langhans' giant cells.

When the Dorothy Reed cells were compared with those from cancerous lesions, it was found that their behavior differed from that of malignant lymphoblasts and monocytes, but resembled that of the malignant myeloblasts, particularly the large multinucleated myeloid cells that multiply in the lymph nodes of certain cancerous lesions that Mider‡ has brought about in mice by means of methylcholanthrene.

From the motion picture studies, it was concluded that the Dorothy Reed cells were myeloid rather than lymphoid or monocytic in origin.

The Respiratory Response of the Dog to Anoxemia. P. R. DUMKE, C. F. SCHMIDT, and H. P. CHIODI (Department of Pharmacology, University of Pennsylvania). These experiments were intended to study the action of anoxia on the respiratory center, to determine the threshold of sensitivity of the chemoreceptors to anoxemia, and to establish the parts played by changes in the oxygen dissociation curve of blood and by the chemoreceptors in producing the additive effects of hypercapnia and anoxemia. Dogs lightly anesthetized with morphine and chloralose were made to breathe in succession room air, pure oxygen, oxygen plus 3.5 % carbon dioxide, 10 to 12 % oxygen in nitrogen and the same plus 3.5 % carbon dioxide before and after denervation of the chemoreceptors. Arterial blood collected during a steady state of each inhalation was analyzed for pH, oxygen and carbon dioxide tension.

* Aided by a grant made to Dr. Warren H. Lewis from the International Cancer Research Fund.

† Rich, Wintrobe and Lewis: *Bull. Johns Hopkins Hosp.*, 65, 291, 311, 1939.

‡ Mider and Morton: *Am. J. Cancer*, 37, 355, 1939.

Inhalation of 10% oxygen produced a definite stimulation of respiration in the normal animal, but after the chemoreceptors were denervated there was only depression of respiration.

Arterial oxygen tensions of 60 mm. of Hg or less were required to produce respiratory stimulation before denervation.

Respiratory depth in the normal dog was consistently greater during inhalation of carbon dioxide in low oxygen than during inhalation of carbon dioxide in pure oxygen. After denervation the hyperpnea of the latter was definitely greater than that of the former. Thus the direct effect of anoxemia on the respiratory center is to depress its response to carbon dioxide.

The increased tolerance to atmospheres low in oxygen following addition of carbon dioxide to the inspired air was found to depend much more on the increased depth of breathing produced by chemoreceptor reflexes than on changes in the oxygen dissociation curve. As measured by the difference between the oxygen tension of the inspired air and that in the arterial blood (ΔpO_2) the chemoreceptor reflexes are approximately four times more important.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

APRIL, 1941

ORIGINAL ARTICLES.

THE DIAGNOSIS OF HEMOPHILIA.*

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HEMOPHILIA is recognized by the triad: inheritance through the female, occurrence only in the male, and a prolonged clotting time. While the diagnosis of hemophilia is usually simple, a number of difficulties may be encountered. A history of bleeding in the family is not always obtainable either because of incomplete records or because the case may be sporadic. Furthermore, another hemorrhagic disease, commonly designated as pseudohemophilia, is also hereditary. Female bleeders are by definition not hemophiliacs, but it is more important to know whether women who suffer from an inherited hemorrhagic condition have the same coagulation defect as a true case of hemophilia. Diagnosis cannot be made solely on a prolonged clotting time, for in severe prothrombinopenia, fibrinogenopenia, heparinemia and extreme thrombocytopenia a retardation of coagulation likewise occurs.

For an indisputable diagnosis of hemophilia, it is essential to have laboratory methods which specifically test the underlying cause of the disease. Recently the writer^{12c} has reviewed the evidence for the conclusion that the delayed coagulation in hemophilia is due to an abnormal resistance of the platelets, which brings about an inadequate liberation of thromboplastin. On this basis, a test was developed which is a modification of the determination of the clotting time of recalcified plasma. The original test was employed as early as 1910 by Addis.¹ A few years later Howell⁸ developed

* Part of this work was presented before the Central Society for Clinical Research, November 4, 1938, Chicago.

it into the standard method, which was unfortunately called by the misleading name, "prothrombin time." Gram⁵ introduced certain useful improvements such as control of temperature and speed of centrifuging. Bancroft and Stanley-Brown² working with Kugelmass and later with the writer³ further simplified the test, and applied it clinically. They, as had former investigators,^{1,6,8,9,11} found that the clotting time of recalcified plasma was prolonged in hemophilia; but a similar finding was often also observed in the plasma of jaundiced patients. Further work by the author led to the finding that in hemophilic plasma, the speed of centrifuging markedly influenced the subsequent coagulation time. From this has developed the following test.

The Test. By venipuncture 4.5 cc. of blood are drawn and mixed immediately with 0.5 cc. of 0.1 M sodium oxalate. The blood is divided into two equal portions. One-half is centrifuged for 5 minutes at a rate not over 1000 r.p.m., while the other half is subjected to a centrifugation of 3000 r.p.m. for 5 minutes in an Angle centrifuge. The clotting time of each specimen is tested as follows: In a small test tube, 0.1 cc. of plasma is mixed with 0.2 cc. of 0.0125 M calcium chloride. The tube is placed in a water bath kept at $37\frac{1}{2}^{\circ}$ C., and tilted occasionally. The exact time required for the formation of a solid clot is recorded.

Solutions: Sodium oxalate 0.1 M.: 1.34 gm. of sodium oxalate is dissolved in 100 cc. of distilled water. Calcium chloride 0.0125 M.: 0.14 gm. of anhydrous calcium chloride and 0.42 gm. sodium chloride are dissolved in 100 cc. of distilled water.

Results. The results obtained with this method yield interesting information. The clotting time of recalcified plasma is much shorter than that of whole blood. The normal for the Lee White test is 5 to 8 minutes, but for recalcified plasma it is only approximately 2 minutes. Apparently in the process of decalcification and subsequent recalcification the stability of the platelets is sufficiently disturbed to bring about extensive destruction of these cells with the liberation of considerable thromboplastin. In undisturbed blood, the disintegration of platelets is very much slower and therefore the coagulation is prolonged. In hemophilic blood, due to the great stability of the platelets, few of these cells undergo lysis, and when the blood is centrifuged at high speed the intact platelets are thrown down leaving the plasma poor in both free and potentially free thromboplastin. With slow centrifugation, however, the platelets remain suspended, and many suffer disintegration subsequent to recalcification. The marked influence that centrifuging has on the coagulation time of hemophilic plasma, in contrast to the slight effect on normal plasma as seen in Table 1, offers therefore a new test for the diagnosis of true hemophilia. It is interesting that if oxalated hemophilic plasma is allowed to stand several hours, the clotting time after the addition of calcium approaches normal. This further suggests that no essential factor is lacking, but that the defect lies in the slow liberation of thromboplastin from the platelets.

TABLE 1.—THE CLOTTING TIME OF RECALCIFIED OXALATED PLASMA AS A TEST FOR HEMOPHILIA.

		Coagulation time.		
		Recalcified plasma.		
		Lee White method, min.	After low centrifugation, sec.	After high centrifugation, sec.
Normal:	I	6	90	105
	II	6	125	145
	III	5	105	130
Hemophilia:	I	38	180	630*-1080†
	II	22	165*-195†	480*-660†
	III	180	330
	IV	40	165*-200†	300*-600†
	V	73	540	900
			180‡	180‡

* Beginning of coagulation.

† Formation of a firm clot.

‡ After standing 6 hours.

The following simple experiments illustrate plainly that hemophilic blood is normal in all respects except for the slow liberation of thromboplastin.

Patient, a white boy age 4. Definite family history of hemophilia.

Clotting time by Lee White Method: 1 hr. 13 min.

Clotting time by Lee White Method in a collodion coated test-tube: 7 hrs.

Experiment 1.

(a)		(b)	
Oxalated hemophilic plasma	0.1 cc.	Oxalated normal plasma	0.1 cc.
Thromboplastin	0.1 cc.	Thromboplastin	0.1 cc.
Calcium chloride 0.025 M.	0.1 cc.	Calcium chloride	0.1 cc.
Clotting time	12 sec.	Clotting time	11½ sec.

Experiment 2.

(a)		(b)	
Hemophilic plasma	0.1 cc.	Hemophilic plasma	0.1 cc.
Saline solution	0.1 cc.	Calcium chloride 0.025 M.	0.1 cc.
Thromboplastin	0.1 cc.	Thromboplastin	0.1 cc.
Clotting time	11½ sec.	Clotting time	14 sec.

Experiment 3.

(a)		(b)	
Hemophilic plasma	0.1 cc.	Hemophilic plasma	0.1 cc.
Saline solution	0.2 cc.	Calcium chloride 0.0125 M.	0.2 cc.
Clotting time	30 min.	Clotting time	13 min.

The first result to be observed is the clotting time. In a glass tube coagulation occurred in a little more than an hour, while in a collodion-coated tube, the time was 7 hours. It has been observed by both Dr. Hirschboeck⁷ and myself that collodion behaves somewhat like the endothelial lining in preserving the fluidity of the blood, *i. e.*, by preventing the liberation of thromboplastin from platelets.

Experiment 1, which is really the quantitative measurement of prothrombin, shows that hemophilic plasma clotted as rapidly as the normal specimen when excess thromboplastin is present thus indicating that the prothrombin is normal. This the author with Stanley-Brown and Bancroft¹³ had shown previously.

In Experiment 2a, the hemophilic plasma containing no added anticoagulant was treated with thromboplastin in the same manner as in Experiment 1 except that no calcium chloride was added. Coagulation occurred in $11\frac{1}{2}$ seconds which agrees with the values obtained in the previous experiment. Obviously, the calcium of the blood is adequate and reactive. When, however, calcium was added to the plasma, the clotting time was prolonged showing that excess calcium has a depressing action on coagulation as was pointed out by the author^{12b} previously.

In Experiment 3a, the hemophilic plasma was diluted with 2 volumes of physiologic saline solution with the result that coagulation which for the undiluted plasma was 73 minutes was reduced to 30 minutes. Significantly when the plasma was diluted with a weak solution of calcium chloride, clotting occurred in 13 minutes. This finding agrees with the observation of Ferguson⁴ that osmotic disturbances within the platelet are under the specific influence of the calcium ions. Thus ionic calcium exerts two diametrically different influences on the speed of coagulation. It depresses the conversion of prothrombin to thrombin, but accelerates the liberation of thromboplastin from the platelets.

On the basis of the concept that hemophilia is basically a disease in which the platelets are abnormally stable, as these simple experiments indicate, an outline for diagnosis by means of laboratory tests can be offered.

Coagulation Time. The Lee White test is the most satisfactory. Clotting times on capillary blood are less delicate since in obtaining the blood a certain amount of contamination with thromboplastin from tissue juices is unavoidable. The clotting time is prolonged in hemophilia, but it varies greatly and may at times approach normal.

The prolonged coagulation time differentiates hemophilia from pseudohemophilia, hemorrhagic purpuras, and scurvy.

Delayed clotting is also found in the prothrombinopenia of obstructive jaundice and of the newborn, in fibrinogenopenia, in anaphylactic shock, and occasionally in severe cytopenic purpura.

Clotting Time of Recalcified Plasma. The test described in this paper is especially useful in doubtful cases of hemophilia. The marked effect of centrifuging on the clotting time, and the gradual decrease in the rate when plasma is allowed to stand can be considered strong positive evidence for hemophilia.

Prothrombin Concentration. The author's quantitative method for prothrombin^{12a} is both simple and accurate. The prothrombin

is normal in hemophilia, but after severe bleeding may become somewhat decreased (rarely below 70%).

A normal concentration of prothrombin differentiates hemophilia from the various types of hypoprothrombinemias and from fibrinogenopenia.

Bleeding Time. The method of Duke, which is in common use, is satisfactory. Care must be taken not to make the cut too deep for fear of striking a large vessel since the test is designed essentially to determine the response of capillaries to the injury from the cut. The bleeding time in hemophilia is normal. Too deep a gash may however cause a false prolonged bleeding time due to the escape of blood from a larger vessel rather than from capillary oozing.

A normal bleeding time differentiates hemophilia from the hemorrhagic purpuras and from pseudohemophilia.

Clot Retraction. Although coagulation is prolonged in hemophilia, when it does occur, the clot undergoes retraction in the normal time of 30 to 60 minutes.

Normal syneresis distinguishes hemophilia from the hemorrhagic purpuras.

Tourniquet Test (Rumpel-Leede or Hess). In hemophilia the tourniquet test is negative, which means that no capillary erythropermeability exists. Since this test is exceedingly useful for recognizing all types of purpuric states, as Madison and Squier¹⁰ have pointed out, its value in differential diagnosis is apparent.

Platelet Count. The number of platelets in uncomplicated hemophilia is well above 100,000 and usually is normal. The platelet count is of limited value, however, since no decrease occurs in pseudohemophilia and in many cases of purpura.

The blood of a true case of hemophilia should show the following:

1. Coagulation time (Lee White test), over 8 minutes (at $37\frac{1}{2}^{\circ}$ C.).
2. Coagulation time of recalcified plasma:
 - a. High speed centrifugation, over 5 minutes.
 - b. Low speed centrifugation, over 3 minutes.
 - c. Clotting time should decrease on standing.
3. Prothrombin concentration (Quick's method), above 70%.
4. Bleeding time (Duke's method), not over 4 minutes.
5. Clot retraction, not over 60 minutes after coagulation occurs.
6. Tourniquet test (Rumpel-Leede technique), not over 4 petechia in specified area.

By means of these simple laboratory tests a positive diagnosis of hemophilia can readily be made. In the typical case with a definite family history, the coagulation time will often suffice. It is the sporadic cases, the female bleeders, and those with a family history of transmission through both male and female progenitors that demand careful study. With a group of tests serving as a criterion for true hemophilia, an improvement in the accuracy of reported cases should be obtained.

With a sharper delineation of the hemorrhagic diseases, more attention should be given to the syndrome which is recognized by the name pseudohemophilia. This condition like hemophilia is hereditary, but in terms of the Mendelian law behaves as a sex-linked dominant factor, whereas in hemophilia the inherited factor is recessive. The disease is transmitted both by males and females and appears in its active form in both sexes. Coagulation time is normal but the bleeding time is intermittently prolonged. Clot retraction is normal, the platelets are not decreased, and the tourniquet test is negative. The first definite description of this disease was made in 1926 by Willebrand,¹⁴ and from the reports that have since appeared, one can conclude that the condition is not uncommon.

Summary. The clotting time of recalcified plasma has been developed into a test for hemophilia. The coagulation time of oxalated hemophilic plasma subjected to high centrifugation is markedly longer than slowly centrifuged plasma. Such a marked difference is not obtained with normal blood.

A simple outline for the differential diagnosis from the other hemorrhagic diseases is outlined. It is based on the facts that in hemophilia the coagulation time of the blood and of the recalcified oxalated plasma is prolonged, but that clot retraction, bleeding time, prothrombin concentration, and the tourniquet test are normal.

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INFECTIOUS MONONUCLEOSIS—A DIAGNOSTIC PROBLEM.

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INFECTIOUS mononucleosis has been known as a clinical entity since 1889, when Pfeiffer⁵ described it under the name of "glandular fever." The practitioner, however, is not always aware of its rela-

tively frequent occurrence or of the severe clinical picture with which this disease may manifest itself. Consequently, some cases of infectious mononucleosis are diagnosed as other infectious diseases, or as common acute infections of the oral cavity. The severe pharyngitis in infectious mononucleosis is the usual source of error, as it often simulates diphtheria.

To illustrate the diagnostic difficulties in some cases of infectious mononucleosis we present here an analysis of 21 cases which were referred with mistaken diagnoses to this hospital during the years 1937-1939.

The 21 cases were referred with the following diagnoses: Diphtheria or observation for diphtheria, 15; epidemic parotitis (mumps), 2; follicular tonsillitis, 2; streptococcal pharyngitis, 1; acute sinusitis, 1.

TABLE 1.—CASES OF INFECTIOUS MONONUCLEOSIS REFERRED OR ADMITTED WITH MISTAKEN DIAGNOSIS.

Case.	Name.	Sex.	Age.	Referred diagnosis.	Admission diagnosis.	Diphtheric antitoxin.	Diphtheria bacilli.		Heterophil anti- bodies, plain absorption.	Total days' ill- ness.	
							Cul- ture.	Tox- icity.			
1	6159	A. S.	M	14	Diphtheria	Follic. tonsill.	Yes	Neg.	N.d.*	1:224 -1:112	13
2	5329	S. G.	M	16	Observ. diph.	Follic. tonsill.	No	Pos.	Neg.	1:448 -1:224	16
3	5932	E. F.	M	23	Observ. diph.	Follic. tonsill.	No	Neg.	N.d.	1:996 -1:448	14+
4	5316	M. W.	F	15	Diphtheria	Diphtheria	Yes	Neg.	N.d.	1:224 -1:112	17
								(nose)			
5	5221	D. S.	F	11	Observ. diph.	Diphtheria	Yes	Pos.	Neg.	1:224 -1:112	15
6	5288	R. C.	M	4	Diphtheria	Diphtheria	Yes	Pos.	Neg.	1:112 -1:56	19
7	1244	H. F.	M	25	Str. pharyng.	Infect. mononuel.	No	Neg.	N.d.	1:56 -1:56	18
8	619	C. Y.	F	21	Diphtheria	Diphtheria	Yes	Neg.	N.d.	1:112 -1:56	18
9	5572	W. M.	M	3	Diphtheria	Str. tonsillitis	Yes	Neg.	N.d.	1:112 -1:56	13
0	5298	R. F.	M	28	...	Acute sinusitis	No	Neg.	N.d.	1:448 -1:224	12
1	4975	R. R.	M	11	Observ. diph.	Infect. mononuel.	No	Neg.	N.d.	1:3584-1:1792	17
2	4639	I. G.	F	16	Diphtheria	Infect. mononuel.	Yes	Neg.	N.d.	1:1792-1:896	18
3	4382	B. N.	M	8	Epi. parotitis	Infect. mononuel.	Yes	Pos.	Neg.	1:56 -1:56	20
4	537	M. M.	F	36	Diphtheria	Infect. mononuel.	No	Neg.	N.d.	1:112 -1:56	28
5	276	N. K.	F	24	Diphtheria	Str. tonsillitis	Yes	Pos.	Neg.	1:112 -1:56	19
6	689	M. S.	F	20	Observ. diph.	Acute tonsillitis	No	Neg.	N.d.	1:224 -1:112	10
7	2433	A. V.	F	20	Epi. parotitis	Observ. parotitis	No	Neg.	N.d.	1:224 -1:112	11
8	2968	E. S.	F	21	...	Acute tonsillitis	No	Neg.	N.d.	1:896 -1:896	16
9	2718	Ad. S.	F	3½	Diphtheria	Diphtheria	Yes	Neg.	N.d.	1:28 -1:14	24
0	3481	L. C.	F	25	...	Acute tonsillitis	No	Pos.	Neg.	Negative	20
1	4133	H. S.	M	23	Diphtheria	Septic sore throat	Yes	Pos.	Neg.	1:1792-1:896	28

* N.d. signifies not done.

In 14 cases the clinical picture was considered sufficiently suspicious of diphtheria to warrant the administration of diphtheria antitoxin upon admission, without awaiting confirmation by culture of the presence of the diphtheria bacillus in the throat. The diagnostic difficulty was further complicated in 7 of these cases by the presence of non-toxic diphtheria-like bacilli in the throats of 6 patients and in the nose of 1 patient. The negative toxicity tests on the isolated bacilli, the hematologic picture, the positive heterophil antibody test and the lack of response to the diphtheria antitoxin helped in establishing the correct diagnosis.

In 5 cases the diagnosis of infectious mononucleosis was made upon admission on a basis of physical findings of pharyngitis with extensive membranous exudate and enlargement of several groups of lymph nodes. The diagnosis was later confirmed by hematologic and serologic findings.

Adequate descriptions of infectious mononucleosis have appeared repeatedly in the literature, and a complete review of the subject was made recently by Bernstein.¹ However, the observations on the 21 cases of this series present some additional clinical and laboratory data of practical significance.

Distribution. 1. *Age.* The youngest patient in this series was 3 years old; the oldest 36 years. The age incidence showed a greater proportion of young adults than children (7 cases between the ages of 3 to 14; 14 cases between the ages of 15 to 36).

2. *Sex.* Although the greater susceptibility of males is mentioned by several authors quoted by Bernstein, the cases in our series were equally distributed between the sexes (10 males, 11 females).

3. *Color.* Four patients in this series were negroes. According to Bernstein, only 1 case of infectious mononucleosis in negroes had been reported in the literature by Longcope.⁴

4. *Regional.* The 4 negro patients who were seen during a single month came from the same district of the city; we were unable to establish any contacts between them, however.

Clinical Picture. The clinical picture of infectious mononucleosis, with special emphasis on the appearance of the throat is presented in some detail, as familiarity with the clinical manifestations often makes diagnosis possible before the laboratory tests are completed.

Duration of Illness. Duration of illness prior to admission to the hospital varied from 1 to 22 days; hospitalization from 6 to 24 days. The total days of illness ranged from 10 to 28.

Subjective Findings. On admission the complaints were: pharyngitis, 20; malaise, 9; anorexia, 8; headache, 7; dysphagia, 8; vomiting, 2; facial edema, 2; lacrimation, 2; chills, 2; nasal discharge, 2; dysarthria, 2.

Objective Findings. The temperature on admission ranged from 99° to 104° F. The duration of the fever varied from 7 to 17 days following the onset of illness. The pulse was elevated in relation to the temperature.

The physical findings are as follows: Tonsillitis: membranous, 20; non-membranous, 1. Lymphadenitis: cervical, 20; axillary, 10; inguinal, 10; popliteal, 2. Palpable spleen, 7. Palpable liver, 3. Edema of the face, 2. Dacryocystitis, 1.

The tonsillitis was the most constant finding. On admission all patients with one exception presented a membrane or an exudate on one or both tonsils. In 18 cases the tonsillitis was considered severe.

In patients severely ill the tonsils were extremely large, almost

meeting in the midline. The membrane or exudate varied in color from ivory-white and grayish white, to grayish yellow. It was adherent to the tonsil and could not be easily removed. In many instances the membrane was granular in appearance, resembling the head of a cauliflower, or a mulberry. The mucosa of the hard palate, the pillars and the fauces in cases with this type of exudate presented a wrinkled, corrugated appearance which is frequently seen in pharyngitis caused by the staphylococcus. The mouth appeared dry, parched, and was glazed with thick, tenacious mucus. In some patients only the tissues immediately surrounding the tonsils were inflamed. With the onset of defervescence the tonsillar exudate loosened up and generally came off *en masse*.

Nine patients showed enlargement of the cervical, axillary and inguinal lymph nodes; in 2 cases the popliteal lymph nodes were also enlarged.

The spleen was palpable in 7 cases. It was firm, not tender and not markedly enlarged. The liver was palpable in 3 cases, and was not tender.

Edema of the face was observed in 2 patients.

Complications. One patient developed dacryocystitis on 9th day of illness.

Secondary anemia developed in 1 case on the 11th day of illness. The patient received no drugs.

No nephritis, jaundice, abdominal pain, purpura or cerebral complications were observed in this series.

Laboratory Findings. *Hematologic.* High total white cell counts of 20,000 or over were observed in 7 patients, the highest total count being 27,800. Four of the 7 patients were children aged 3 to 14 years. In the 4 children the high total white cell counts occurred in the 1st, 3d, 5th and 6th days of illness; in the 3 adults on the 10th, 11th and 12th day of illness. In individual cases the highest total white blood cell counts followed the same pattern: below the age of 15 the highest total counts occurred during the 1st week of illness; in adults who were in the hospital during the 1st and 2d week of illness the highest total counts were observed during the 2d week.

The blood smears were stained with the MacNeal tetrachrome stain which permits an adequate differentiation of monocytes from abnormal large lymphocytes. Duplicate smears were stained with the Goodpasture peroxidase stain, often with subsequent staining of the same slide with the tetrachrome, in order to bring out the peroxidase positive granules of the monocytes.

The highest percentage of lymphocytes found in this series was 87%, in an 11-year-old child, on the 8th day of illness. The highest absolute number of lymphocytes observed per 1 c.mm. was 17,675 (75% lymphocytes), in an adult, on the 12th day of illness. The highest percentage of abnormal lymphocytes (45%) with amitotic

division of lymphocytes in the peripheral blood, was seen on the 10th day of illness in an adult who had 61% of total lymphocytes.

The "shift to the left" and the occurrence of toxic granules in the neutrophils was more pronounced in children than in adults.

Secondary anemia developed in 1 patient who received no drugs while in the hospital (Case R. C.). On the 6th day the blood count showed 4,700,000 red blood cells and 75% hemoglobin. On the 11th day his red blood cells fell to 3,180,000, the hemoglobin was 55%, and nucleated red blood cells appeared in the smear. This was the patient with the highest white cell count in this series (27,800).

Serologic. The heterophil antibody test was performed by the Davidsohn method^{3a,b} in preference to the original technique of Paul and Bunnell.⁵ The highest level of agglutination was controlled microscopically, by examining a drop of the suspension on a slide (without a cover) with a low power objective. The differential method of Davidsohn was adapted because the majority of our patients with infectious mononucleosis received the horse serum in the form of diphtheria antitoxin. Consequently there was a possibility of the presence of Forssman antibodies in their blood, either from the horse serum in their blood stream, or as a result of serum sickness. Absorption of Forssman antibodies by the suspension of guinea-pig kidney, as recommended by Davidsohn, eliminates entirely the Forssman antibodies from the blood serum, but removes only a part of the heterophil antibodies. The agglutination titer was 1:56 (with a drop to 1:28 after absorption) was considered positive.

Bernstein pointed out that the titer of heterophil antibody does not change after administration of horse serum. One of our patients (B. N.) showed a titer of 1:56, and no absorption by the suspension of guinea-pig kidney suspension; after administration of diphtheria antitoxin the titer remained unchanged.

The heterophil antibody reaction was positive in 19 of our 21 cases (90%), negative in 1 (adult) and doubtful in 1 (child, Ad. S., titer 1:28 with a drop to 1:14 after absorption). The high percentage of positive reactions in our series corresponds to the findings of Bernstein (92% of positive reactions). Other authors observed a lower incidence of positive heterophil antibody reactions in infectious mononucleosis (Rosenthal and Wenkebach⁷).

The heterophil antibody reaction usually becomes positive during the 1st week of illness (Bernstein). In 1 of our cases it was found to be positive on the 2d day of illness, the titer (1:56) remaining unchanged on the 4th and 5th day. In another case, however, the reaction was negative on the 7th day, but became positive (1:112) on the 8th day. The height of the titer in individual cases was usually reached during the first week of illness. However, in 1 case the titer which was 1:56 on the 6th day rose to 1:224 on the 9th day.

The highest titer observed in this series was 1:3584, in a boy of 11, on the 8th day of illness.

We can confirm the observation of Bernstein that the titer of a positive serum stored in an icebox remains unchanged for months. Positive sera thus may be kept in storage and used as control in performing the heterophil antibody test with unknown sera.

False positive Wassermann and Kline reactions were observed in 4 cases with no history or clinical findings suggestive of syphilis. In these cases subsequent tests showed either negative results within a few days, or less sensitive reactions became negative, while the more sensitive reactions still showed positive results at the time the patients were discharged from the hospital.

Case	Age	Day of illness	Test	Day of illness	Test
H. P.	25	11	Wassermann: Alcohol. antig. 0 Cholest. antig. =	17	
M. W.	15	5	Kline diagn. positive Wassermann: Alcohol. antig. 3+ Cholest. antig. 4+	17	Kline diagn. = All tests negative
Ad. S.	3½	7	Kline diagn. { Strongly Kline exclus. { positive Wassermann: Alcohol. antig. 1+ Cholest. antig. 2+	22	All tests negative
H. S.	23	5	Kline diagn. } Positive Kline exclus. } Wassermann: Alcohol. antig. 3+ Cholest. antig. 4+	17	Wassermann: Alcohol. antig. 0 Cholest. antig. 2+ Kline diagn. } Kline exclus. } Positiye
			Kline diagn. { Strongly Kline exclus. { positive		

There was no correlation between the titer of the heterophil antibody reaction and the presence of false-positive reactions for syphilis.

Bacteriologic. Throat smears were examined for Vincent's spirilli and fusiform bacilli in 15 cases. Scattered Vincent's microorganisms were found in 6 cases. Only 1 of the patients (M. W.) showing the presence of spirilli had false-positive Wassermann and Kline reactions.

Non-toxic bacilli of the diphtheria group were found in 7 cases (6 in the throat, 1 in the nose). Their presence delayed the correct diagnosis until the completion of the toxicity tests.

Other bacteria cultured from the throat were *Strep. hemolyticus*, *Strep. viridans*, *Staph. aureus* and *Staph. albus*.

Differential Diagnosis. The diagnosis of infectious mononucleosis is not difficult, if the possibility of that disease is kept in mind. While the clinical picture may not always be typical, a hematologic study over a period of several days, and a positive heterophil antibody reaction helps to confirm the diagnosis.

Since the infectious mononucleosis is primarily a pharyngeal infec-

tion, the differential diagnosis must include: *a*, diphtheria, *b*, acute tonsillitis, *c*, ulcerative sore throat (superficial and Vincent's angina), *d*, streptococcus pharyngitis, *e*, staphylococcus pharyngitis, *f*, agranulocytic angina, and, *g*, acute lymphatic leukemia with pharyngitis.

In view of widespread lymphadenopathy, acute lymphatic leukemia must be considered. In the early stages of infectious mononucleosis, when only the cervical lymphadenitis may be markedly enlarged the question of mumps may arise, as the enlarged cervical lymph nodes may simulate the enlargement of the parotid glands.

Diphtheria. Early differentiation from diphtheria is especially desirable, in order to avoid administration of the antitoxin and sensitization of the patient to the horse serum.

The typical appearance of the throat in diphtheria, with its adherent grayish membrane, is well known. On removal the membrane leaves a bleeding surface. However, in atypical cases the diagnosis is at times very difficult without bacteriologic confirmation. If the patient's general condition permits a delay in the administration of the antitoxin, a throat smear may be examined for the presence of the diphtheria bacilli, and rapid cultures (the 4-hour method of Brahdy, Lenarsky, Smith and Gaffney²) for the presence of the diphtheria bacilli may be done before the administration of the antitoxin. However, if the patient presents a clinical picture suggestive of toxic diphtheria, no time should be lost in the administration of the antitoxin, and all the laboratory work may be done later.

If diphtheria-like bacilli are found in the throat or nose cultures in a patient who does not respond to the antitoxin, the isolated bacillus must be tested for toxicity and the possibility of infectious mononucleosis must be considered. The diagnosis can usually be made by hematologic and serologic examinations before the completion of the toxicity test. The blood picture in diphtheria is usually one of neutrophil leukocytosis. However, abnormal lymphocytes occur occasionally in children. The heterophil antibody reaction is negative despite the administration of the antitoxin, if the differential method of Davidsohn is used.

Two typical cases of infectious mononucleosis referred to the hospital with the diagnosis of diphtheria are presented.

Case Reports. CASE 1.—W. M. (5572.) *Referred as diphtheria. Throat culture negative for diphtheria bacilli.* The patient, a 3-year-old white male, was admitted on the 4th day of illness complaining of fever, anorexia, pains in the joints and sore throat. The admission diagnosis was: Streptococcus tonsillitis; possible diphtheria. The temperature on admission was 103.4° F.; pulse, 140. The patient was acutely ill, with rapid respirations, flaring alæ nasæ and oral fetor. The tonsils were large, severely inflamed and covered with a thick grayish yellow plastic exudate. The exudate was present also over the posterior pharyngeal wall. There was a moderate serous nasal discharge. The lids of both eyes were mildly edematous, tender and puffy.

The cervical, axillary and inguinal lymph nodes were enlarged and discrete. The liver was palpable—1 finger below the costal margin, but the

spleen was not palpable. The patient received 20,000 units of diphtheria antitoxin and, in addition, 6000 units of scarlet fever antitoxin.

On the 5th day of illness, the membrane persisted.

On the 6th day of illness, the spleen was palpable and the appearance of the throat and of the tonsillar membrane was somewhat improved. The blood count showed 22,600 white blood cells with 32% neutrophils and 66% lymphocytes, of which 52% were abnormal. The heterophil antibody test was positive 1:112 (after absorption—1:56).

On the 10th day of illness, the left tonsil showed a crater-like excavation, covered with a yellowish membrane.

On the 11th day of illness, the cervical lymph nodes were no longer palpable. The axillary and inguinal nodes were still present. On the 12th day of illness, the tonsils no longer showed evidence of an exudate.

The temperature returned to normal by lysis on the 13th day of illness.

CASE 2.—R. C. (5288.) *Referred as diphtheria. Non-toxic diphtheria-like bacilli in the throat. Secondary anemia in the course of infectious mononucleosis.* The patient, a 4-year-old colored child, was admitted on the 5th day of illness, as a case of diphtheria. The complaints were: sore throat, headache, fever and dysphagia. On admission the temperature was 103.2° F.; pulse, 136. The patient was undernourished, underdeveloped and acutely ill. Both tonsils were very large, inflamed and covered with a thick gray foul-smelling membrane, adherent to the substance of the tonsil. There was a bleeding when the membrane was removed. The cervical and inguinal lymph nodes were enlarged. The patient was given 20,000 units of diphtheria antitoxin. The blood count on admission showed 27,800 white blood cells with 57% lymphocytes.

On the 6th day of illness, there was no response to the antitoxin. A blood count showed hemoglobin, 75%, and red blood cells, 4,970,000. The throat culture taken on the preceding day showed the presence of diphtheria-like bacilli (the bacilli were subsequently found to be non-toxic). The heterophil antibody reaction was positive 1:112 (after absorption—1:56).

On the 8th day of illness, the left tonsil showed a deep ulceration with a sharp line of demarcation against normal tonsillar tissue. A blood count showed 17,000 white blood cells, with lymphocytes 54%, of which 13% were abnormal.

On the 9th day of illness, the throat began to clear. The temperature became normal and the membrane had completely disappeared by the 12th day of illness.

On the 11th day of illness, the hemoglobin was 55%, red blood cells, 3,180,000, with normoblasts in the smear. The patient received no drugs while in the hospital. Blood transfusions were given.

Acute Follicular Tonsillitis. In early stages of infectious mononucleosis the exudate may be follicular in character (Case B. N.). The differentiation from the acute follicular tonsillitis is possible only with the aid of blood studies.

Ulcerative Stomatitis. 1. *Superficial.* Superficial ulcers are present on the swollen tonsils, often on the soft palate and in the pharynx. An exudate or a membrane may be present. The blood count is within normal limits.

2. *Vincent's Angina.* One or both tonsils may be covered with a grayish white or dirty-yellow exudate often superimposed on a slough. A clear-cut ulcer remains after the separation of the slough. The diagnosis is established by the finding of numerous spirilli and fusiform bacilli in smears from the throat. The Wassermann and

Kline reactions may be positive, but the heterophil antibody reaction is negative. The blood morphology shows no deviation from normal.

Streptococcal and Staphylococcal Pharyngitis. In both types of infection a thick, yellowish or whitish-gray exudate may be present over the tonsils, soft palate and posterior pharyngeal wall. In our experience, in the staphylococcus infection the exudate may be granular, mulberry-like, and resembles particularly the exudate in infectious mononucleosis.

A neutrophil leukocytosis is present in both streptococcus and staphylococcus pharyngitis.

Agranulocytic Angina. The tonsils present a dirty-gray or blackish appearance, as if covered with a membrane. This appearance is, however, due to necrosis of the substance of the tonsils and not to a superimposed exudate. The posterior pharyngeal wall and the larynx may present a similar appearance. A history of medication injurious to the hemopoietic system can often be elicited. The diagnosis is established by a blood count showing leukopenia with neutropenia.

Acute Lymphatic Leukemia, With or Without Pharyngitis. The differential diagnosis may be difficult, as a widespread lymphadenopathy and abnormal lymphocytes in the blood may be present in both lymphatic leukemia and infectious mononucleosis. The heterophil antibody reaction is negative in acute lymphatic leukemia, although it has been reported to be positive in a case of aleukemic leukemia (Paul and Bunnell⁶). Examination of bone marrow may be necessary, if the heterophil antibody reaction is negative.

Epidemic Parotitis.—The differentiation of infectious mononucleosis from the epidemic parotitis is facilitated by the presence of widespread lymphadenopathy and by the positive heterophil antibody reaction.

A case of infectious mononucleosis referred to the hospital with the diagnosis of mumps is presented.

CASE 3.—B. N. (4382.) *Referred as epidemic parotitis. Non-toxic diphtheria-like bacilli in the throat.* The patient, an 8-year-old white male, was referred to the hospital as a case of epidemic parotitis, on the 1st day of illness. The complaints were: a swelling over the left side of the face and a moderate epistaxis that morning. On admission the tonsils were enlarged and presented a white follicular exudate. The pharynx was inflamed, and oral fetor was present. The anterior and posterior cervical lymph nodes were enlarged on both sides, with swelling below and behind the angle of the jaw on the left. The parotid gland was not definitely involved. The axillary and inguinal lymph nodes were palpable. The edge of the spleen was palpable. A soft systolic apical murmur was auscultated. The temperature was 104°, pulse, 124. A tentative diagnosis of infectious mononucleosis was made.

The blood count done on the same day showed 20,750 white cells with 73% lymphocytes and 27% neutrophils. The heterophil antibody tests on the 2d and 4th days of illness were positive 1:56, with no change of the titer after absorption.

The swelling of the left side of the face during the 2d and 3d days of illness increased.

On the 4th day of illness throat cultures for diphtheria-like bacilli were positive. The Schick test was negative. Because of the spread of the exudate on the right tonsil and the toxic state of the patient, 20,000 units of diphtheria antitoxin were given.

The blood count on the 5th day of illness showed 11,500 white cells, 65% lymphocytes, of which 49% were abnormal. The heterophil antibody test remained unchanged.

On the 6th day of illness the facial swelling began to decrease and the exudate on the tonsil began to peel away. The general condition improved rapidly.

Subsequent examination showed that the diphtheria-like bacilli from the throat were non-toxic. The patient was discharged on the 16th day of illness with complete subsidence of adenopathy.

Conclusions. 1. Patients with infectious mononucleosis often are severely ill. An extensive pharyngitis is usually present, often simulating diphtheria.

2. Cervical lymphadenopathy in early infectious mononucleosis may occasionally simulate mumps.

3. Early differentiation of infectious mononucleosis from diphtheria is desirable in order to avoid unnecessary administration of diphtheria antitoxin and sensitization of the patient to horse serum.

4. Cases of clinical diphtheria which do not respond to antitoxin must be investigated hematologically and serologically for the possibility of infectious mononucleosis.

5. Non-toxic diphtheria-like bacilli may be present in the nose and throat of patients with infectious mononucleosis.

6. In children the highest white blood counts are observed during the 1st week of illness, in adults in the 2d week of illness.

7. The heterophil antibody reaction was positive in 90% of 21 patients of this series.

8. The titer of sera showing positive heterophil antibody reactions remains constant for months, if the sera are stored in an icebox. Positive sera may be used as control in performing the test with unknown sera.

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OBSERVATIONS ON INFECTIOUS MONONUCLEOSIS.

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DURING the course of our efforts to determine the mechanism of infectious mononucleosis, we have encountered certain interesting phenomena which we propose to discuss here. They concern the

two characteristic features of this disease; the hematology and the serology. These manifestations alone differentiate the entity of infectious mononucleosis from others presenting a similar clinical picture. Obviously then, investigations concerning these aspects of the illness are indicated in the attempt to ascertain its nature.

It is generally held that the hematologic and serologic findings in infectious mononucleosis are pathognomonic. However, a few previously recorded observations may seem contrary to this opinion. On one hand, the incidence of positive Paul-Bunnell reactions associated with the typical lymphocytic picture has not been 100%. Thus Paul¹³ found the test positive in 90% of a series of 50 cases and Rosenthal and Wenkebach¹⁶ found only 50% to be positive. Several reasons for these results might be possible: *a*, faulty serologic technique; *b*, failure to make serial heterophil determinations and thus miss the appearance of the antibodies; *c*, improper interpretation of the differential count. Whatever the reason, the failure to obtain a positive heterophil reaction when the typical cells of infectious mononucleosis are found has given rise to the hypothesis that one may be dealing with an entity separate from infectious mononucleosis.

On the other hand, there are several cases in the literature^{4,7,14,24} in which the heterophil antibodies were increased without clinical or hematologic evidence of infectious mononucleosis. But as the differential adsorption tests with guinea-pig kidney or beef erythrocytes were not done in some instances, the antibodies were not conclusively proven to be those of infectious mononucleosis. The 2 cases of this nature presented by Stuart *et al.*²⁴ were shown to have the typical antibodies during recovery from meningococcal meningitis which had been treated with immune horse serum. Serum sickness with its characteristic heterophil antibody had also appeared in both patients prior to the development of those of infectious mononucleosis. One of these cases had some form of an intercurrent infection on the day the complete Paul-Bunnell test was positive. Such an event during the course of infectious mononucleosis has been shown to obliterate the blood picture of this disease.^{9,11,12} Hence, for all practical purposes, a positive Paul-Bunnell test is always associated with characteristic lymphocytes.

The question remaining is then, does the presence of these abnormal cells without an elevated heterophil titer indicate infectious mononucleosis? Are they a reflection of a previous episode of this disease, for Farley¹⁰ found them to be present 10 years after the acute stages had subsided in 1 case. Or are these cells an "irritation" form of lymphocyte which are liberated into the blood stream under certain conditions? We shall return to these questions after the presentation of our data.

Material and Methods. Blood counts and blood for the heterophil test were obtained as soon as possible from the college students on their appear-

ance at the college dispensary with suggestive signs and symptoms. These tests were repeated as frequently as practical under these conditions. The differential counts were performed by the author. The heterophil tests were made in two laboratories: those in which hot and cold titers are recorded, were done at the laboratory of the State of Connecticut; the remainder at the New Haven Hospital. The majority of heterophil tests were performed in the former laboratory as differential adsorptions could be done there. The reciprocals of the dilutions are recorded in the following tables. It has been shown that the increased heterophil antibodies of infectious mononucleosis are not adsorbed by tissues containing the Forssman antigen such as guinea-pig kidney; whereas the true Forssman antibody and the heterophil antibody of serum sickness are adsorbed by such tissues.

Results. The cases have been segregated into three classes for obvious reasons. The first group consists of patients who presented the clinical findings of infectious mononucleosis but who lacked an heterophil response of any significant degree. An absolute lymphocytosis is to be noted in each case and the number of abnormal forms is in general less than the figures recorded in the other groups.

GROUP I.

Day of disease.	W.B.C.	P.	L.	Abn. L.	M.	E.	B.	Paul-Bunnell.
J.S. 4	11,000	80	16	0	3	1	0	
5	9,700	60	37	3	3	0	0	
6	8,400	53	37	18	4	6	0	H.(-): C.(-)
8								H.(-): C.3+ 10;1+ 40
10	12,000	48	41	17	5	6	0	
17								H.(-): C.4+ 10;2+ 20
30	9,000	64	29	0	4	3	0	H.(-): C.(-)
E.D. 6	12,000	54	38	5	6	1	1	H.(-): C.4+ 10;3+ 40
9	14,100	51	45	15	4	0	0	
12								H.(-): C.4+ 20;2+ 40
17								H.1+ 5: C.4+ 10;1+ 40
37		39	52	4	9	0	0	H.(-): C.3+ 10;1+ 20
R.M. 6								Before adsorption with guinea-pig kidney. After adsorption.
8	10,500	63	35	4	2	0	0	H.4+ 10;3+ 20;2+ 40: C.4+ 20;3+ 40;1+ 80:
10	9,400	62	34	3	4	0	0	
15	8,900	53	37	8	8	1	1	H.4+ 10;2+ 20;1+ 40: C.4+ 80;2+ 160: H.4+ 10;3+ 20;1+ 40: C.4+ 80:
22								(-) 2+ 5;1+ 10: (-) 1+ 5:
R.S. 3	13,000	66	20	5	12	1	1	
4								H.2+ 5;1+ 10: C.4+ 10;3+ 20;1+ 40: H.3+ 5;1+ 10: C.4+ 80;1+ 160: H.2+ 5;1+ 10: C.4+ 40;3+ 80;1+ 160:
14	10,800	35	60	25	4	1	0	
21	11,000	36	61	22	2	1	0	

H. means hot titer; C. cold titer. Figures are the reciprocals of the serum dilutions.

R. S. was said to have had "glandular fever" exactly 2 years before this episode, but no blood count or heterophil test was done.

The adsorption test with guinea-pig kidney was performed in Group I on R. M. only, as the hot titers in the other instances were not elevated above normal values. The significance of the residual agglutinative activity of R. M.'s serum at 4° C. after adsorbing with guinea-pig tissue has not been determined.

The second group consists of 2 cases of infectious mononucleosis on which heterophil determinations were made very early in the course of the disease. The significant points in these cases are: 1, the increase of Forssman antibodies before the development of those of infectious mononucleosis; and 2, the greater percentage of abnormal lymphocytes than in the previous group.

GROUP II.

Day of disease.	W.B.C.	P.	L.	Abn.	L.	M.	E.	B.	Paul-Bunnell.	
									Before adsorption with guinea-pig kidney.	After adsorption.
H.D. 12	10,700	47	47	15	6	0	0	0	H.2+ 5;1+ 10 C.4+ 10;2+ 20;1+ 40	(-) (-)
18									H.3+ 5;2+ 20;1+ 40 C.4+ 40;3+ 80	(-) (-)
28	11,600	32	63	27	5	0	0	0	H.4+ 20;2+ 40:: C.4+ 20;2+ 160;1+ 320::	2+ 10;1+ 20 3+ 10;2+ 20; 1+ 40
C.A. 4	10,000	38	57	28	5	0	0	0	H.4+ 40;2+ 160:: C.4+ 40;2+ 320::	(-) (-)
7									H.4+ 80;3+ 160;1+ 320: C.4+ 40;2+ 320::	4+ 80;1+ 320 4+ 40;3+ 320; 1+ 640
8	15,000	29	67	47	3	1	0	0		
15	14,500	30	66	36	4	0	0	0		
17									H.4+ 80;2+ 320 C.4+ 160;3+ 320;2+ 1280	4+ 160;2+ 320 4+ 320;2+ 640;3+ 2560

We reproduce the findings of the third group to afford some comparison with the above cited disclosures. In particular, one should note the higher percentage of abnormal lymphocytes than in Group I and the variable time of appearance of the heterophil antibodies from the onset of symptoms.

We have not included in this report our findings in a number of cases with upper respiratory infections, acute pharyngitis, or sinusitis, solely because serial blood counts and Paul-Bunnell reactions were not complete in these instances. However, 15 heterophil determinations were performed at various times during these afflictions and the results were all negative. A study of the blood smears from many of these cases showed clearly, on the other hand, cells characteristic of infectious mononucleosis which comprised 1% to 10% of the differential count. This observation confirms the similar findings of others.^{2,8,24}

Discussion. Our data present two striking facts and provoke considerable speculation. If it is accepted that the curious lymphocytes of infectious mononucleosis are found in the circulation in health and other diseases, it is evident that a positive Paul-Bunnell reaction only occurs when these cells form a large proportion of the differential white count. Secondly, we confirm the observation of Sohler *et al.*¹⁸ that the titer of the normal Forssman heterophil antibody may increase in infectious mononucleosis before the development of those heterophil antibodies typical of this disease. This

latter statement is perhaps not entirely justifiable, as we have been unable to test these sera with beef erythrocytes.*

GROUP III.

GROUP III.										Paul-Bunnell.	
Day of disease.	W B.C.	P.	L. Abn.	L. M.	E.	B.		Before adsorption.	After adsorption.		
J.M. 8	13,750	36	50	11	10	4	0				
10								+4			
11	11,600	27	51	32	20	2		H.4+ 80;2+ 320::	4+ 40;2+ 320		
21								C.4+ 160;2+ 640::	4+ 160;1+ 640		
								H.2+ 5;1+ 10			
93								C.4+ 10;1+ 40			
R.F. 8	10,000	53	43	40	3	1	0	H.4+ 40;3+ 80;2+ 160; 1+ 320;	3+ 10;2+ 20; 1+ 40		
								C.4+ 160;2+ 320; 1+ 640::	4+ 40;3+ 80; 2+ 160		
25	15,600	42	53	5	5	0	0	H.4+ 20;2+ 80;1+ 160::	2+ 20;1+ 40		
29								C.4+ 80;3+ 160;2+ 640; 1+ 1260;	4+ 40;3+ 80; 1+ 320		
C.F. 18	25,000	7	91	76	0	2	0	H.4+ 10;3+ 40;2+ 80::	4+ 160;2+ 320		
								C.4+ 20;3+ 40;1+ 80::	4+ 320;2+ 640		
47	14,200	44	48	4	6	2	0	H.2+ 5;1+ 20;	(-)		
								C.4+ 5;3+ 10;2+ 40; 1+ 160	(-)		
J.A. 5	6,250	60	34	3	6	0	0	+8			
7	7,250	42	53	12	5	0	0				
9								+128			
10	14,350	7	88	67	5	0	0				
14								+256			
16	17,550	19	76	42	4	1	0				
E.C. 7	16,400	12	88	60	0	0	0	H.4+ 320;2+ 2560::	4+ 160;3+ 640; 2+ 1280; 1+ 2560		
								C.4+ 2560::	4+ 160;3+ 2560		
19	12,100	21	72	41	6	1	0	H.4+ 320;3+ 640; 1+ 1280::	4+ 320; 3+ 1280; 2+ 2560		
								C.4+ 320;3+ 1280; 2+ 2560::	4+ 2560		
C.E. 3	6,100	54	35	6	8	3	0				
5	4,500	78	12	?	10	0	0	H.4+ 5;1+ 10			
								C.4+ 10;3+ 40;1+ 80:			
7	4,800	58	32	12	10	0	0				
9	15,000	10	80	?	10	0	0				
15	8,900	11	84	38	3	0	2	H.4+ 10;3+ 40;2+ 80:	3+ 5;2+ 10; 1+ 40		
								C.4+ 160;2+ 320::	4+ 80;3+ 160; 1+ 320		

The nature of the characteristic antibodies of infectious mononucleosis has been the subject of much argument. The investigations of several authors^{1,3,6,19,20,24} present evidence that these immune bodies do not fulfill the requirements of the true Forssman heterophil antibody. The same has been shown to be the case for the increased heterophil antibodies of serum sickness^{1,6,23} despite the fact that the injected sera almost always contain the Forssman

* A sample of C.A.'s serum withdrawn on the 4th day of disease, and which had been kept at 4° C. for 6 weeks, was sent to Dr. K. M. Wheeler of the Connecticut State Department of Health. He very kindly subjected the sample to various procedures which indicated beyond doubt that the antibodies were those of infectious mononucleosis and not of the Forssman type as we have described. This raises an interesting point—was the original serologic technique at fault or did this change occur *in vitro*? On this same day, 20 cc. of C.A.'s fresh whole blood was given intraperitoneally to a Macacus. No significant clinical, hematological or serological changes occurred in the monkey in 4 weeks.

antigen. Heterophil antibodies are also augmented in patients receiving immune horse serum who do not develop serum sickness.⁵ Whether these antibodies are of the Forssman class is not known, as differential adsorption tests have never been reported in this connection. When rabbit serum, which does not contain the Forssman antigen, or horse serum from which this antigen has been removed are used, an elevated heterophil titer is produced.^{15,17} Unfortunately again the differential adsorption tests have not been made. We think it is significant, however, that C. A. of Group II showed an increase of the heterophil antibodies adsorbable by guinea-pig kidney on the fourth day of illness; whereas 3 days later they were not.*

The whole question of antibody production in infectious mononucleosis is obscure and complex. Non-specific bacterial agglutinins for typhoid, paratyphoid, undulant fever, and so on appear from time to time. Falsely positive Wassermann, Kahn, and Eagle reactions are frequent. Two mechanisms for these findings may be postulated: 1, the antibodies may be those normally present or previously acquired in some manner; 2, the chemical and spatial structure of the antigens of the above conditions and infectious mononucleosis may be very closely related. Regardless of the means, the results are non-specific. With the former mechanism, a liberation of preformed antibodies could be thought to occur. In the second instance, either "typhoid-like" immune bodies might be produced by the antigen of infectious mononucleosis; or the heterophil antibody itself might be capable of agglutinating the bacteria and so on. Either mechanism could also explain the observation of the Forssman antibody in our cases.

What seems more logical, perhaps, is that the heterophil antibodies of infectious mononucleosis represent certain alterations in the molecular complex of the Forssman antibody. That is, the presence or development of the latter is essential for those of infectious mononucleosis. Davidsohn⁵ has presented evidence that a similar state of affairs may determine the heterophil response to immune horse serum. Stuart *et al.*^{21,22} likewise showed that the ability to produce specific human A agglutinins in rabbits depends upon the presence of preformed A agglutinins in their sera. Perhaps it is mere coincidence, but in the case of C. A. it should be noted that the heterophil titers before the adsorption tests were carried out are almost identical, although 3 days supervened between the titrations.*

Prior to the presentation of our data, we ended the introduction with some unanswered questions. We still feel unable to settle these queries conclusively. It is our personal opinion that the finding of abnormal lymphocytes in states without a positive Paul-Bunnell test does not indicate a previous state of infectious mononucleosis. Possibly, the cells are irritative in origin and appear in response to a variety of foreign proteins. Under certain conditions this reaction

* See footnote on preceding page.

may be exaggerated and the typical picture of infectious mononucleosis develops. Whether there is a direct connection between the curious cells and antibodies of the disease is a problem demanding investigation.

Summary. We have presented evidence of the following phenomena to be found in infectious mononucleosis. Forssman heterophil antibodies are probably increased prior to the development of the heterophil antibodies of this disease and possibly are essential for their appearance. The typical lymphocytes of infectious mononucleosis are frequently found in disease entities in which a positive Paul-Bunnell has not been obtained. Only when the proportion of these abnormal cells is considerable does one find an elevated heterophil titer.

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STUDIES OF THE CELL IN NORMAL AND ARTHRITIC BOVINE CARTILAGE.*†

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Two years ago the study of hypertrophic arthritis was undertaken in our laboratory. Believing that hypertrophic arthritis is the result of cartilage cell deterioration, we recognized that progress

* Supported in part by the Bryn Mawr Fund for the Investigation and Treatment of Arthritis.

† Presented before the American Orthopaedic Association, May 7, 1940, Kansas City, Missouri.

could be made only by expanding our knowledge of articular cartilage. More particularly, it was considered essential to study the action of the normal cartilage cell. Experiments were devised to this purpose.

This paper has for its purpose the analysis and interpretation of the chemical and morphologic data accumulated during our investigations. The details of our work are appearing in publications devoted to biochemistry. It is felt that such correlation as may exist between the experimental work and the clinical problems should be presented in an interpretive form.

Technique. Bovine articular cartilage was chosen as the experimental material. Fresh material was obtained from local abattoirs. The age, sex and breed of each specimen was noted and the examination of the material began within 60 minutes after slaughtering. Slices of cartilage were cut from the distal articulations of the metacarpals and metatarsals. Some of these slices were fixed, later to be embedded, cut, stained and studied histologically. The metabolism of the remaining slices were studied by the manometric technique of Warburg. Thus it was possible in each experiment to compare the biochemical determinations with the histologic findings of contiguous slices of cartilage and to correlate both results with age, sex and breed. It is of importance to record that in the older cattle degenerative changes of the articular cartilage were present. These changes were characteristic of hypertrophic arthritis.

The material studied was separated, according to age, into three groups:

- I. Young—6 weeks to 6 months.
- II. Adult —1 year to 7 years.
- III. Old —8 years and older.

Histologic Examination. Of the histologic examinations made, but two phases will be discussed here: A, Cartilage cell counts; B, Nuclear measurements.

A. Cell Counts. To determine the *cellular density* of articular cartilage the number of cells per unit volume of tissue were counted. The unit of volume used was the cubic millimeter. Over 250,000 cells were counted. The cellular densities thus obtained were checked against the breed, sex, and age of the animals. No correlations were possible between cellular density and the breed or sex of the animal. A definite correlation could be made between cellular density and the age of the animal. It was found that a direct and proportionate diminution of cellular density accompanied advancing age.

TABLE 1.—AVERAGE CELLULAR DENSITY OF ARTICULAR CARTILAGE.

	Cells per c.mm.
I. Young	133,000
II. Adult	47,000
III. Old	34,000

Expressing these findings in terms of percentage by assigning 100 to the average cellular density of young animals, it was possible

to show more graphically the diminution of the number of cells per unit volume of tissue with advancing age.

- I. Young—cellular density equals 100%.
- II. Adult —cellular density equals 35%.
- III. Old —cellular density equals 25%.

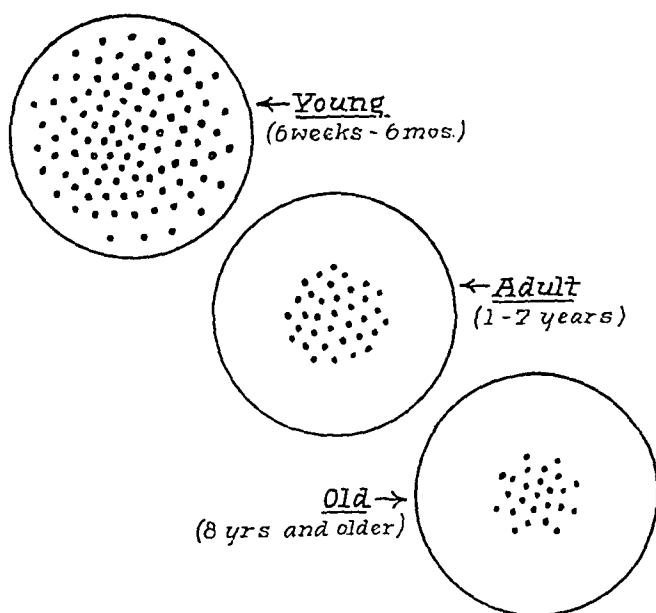


FIG. 1.—Number of cartilage cells per unit volume of tissue.

B. Nuclear Measurements. By projection and direct measurement the sizes of over 5000 cartilage cell nuclei were obtained. From these measurements the *volumes* of the nuclei were computed. It was found that:

1. The average nuclear volume was 90 cubic microns.
2. The average nuclear volume did not change with age.
3. Insufficient data did not warrant other conclusions although there was indication that average nuclear volume varied with the breed of cattle.

By combining the data cited in A and B, it was possible to compute that each nucleus in the young animal was surrounded by 8000 cubic microns of tissue. In other words, the relation of the nuclear volume to the volume of surrounding tissue was as 90 to 8000, or 1 to 90. This finding further illustrated the sparsity of cartilage cell distribution even in the very young animal.

Similar computations showed that in adult animals each cartilage nucleus was surrounded by 20,000 cubic microns of extranuclear tissue. In old animals the amount of tissue surrounding each nucleus amounted to 33,000 cubic microns. Hence it can be stated

that the extranuclear tissue was 250% greater in adult and 400% greater in old animals when compared to that present in young animals.

TABLE 2.—RELATION OF NUCLEAR VOLUME TO EXTRANUCLEAR TISSUE VOLUME.

I. Young	1 to 90
II. Adult	1 to 200
III. Old	1 to 370

Further analyzing the above data the internuclear distances were determined.

TABLE 3.—INTERNUCLEAR DISTANCES.

	Microns.
I. Young	20.0 (100%)
II. Adult	27.2 (136%)
III. Old	32.1 (160%)

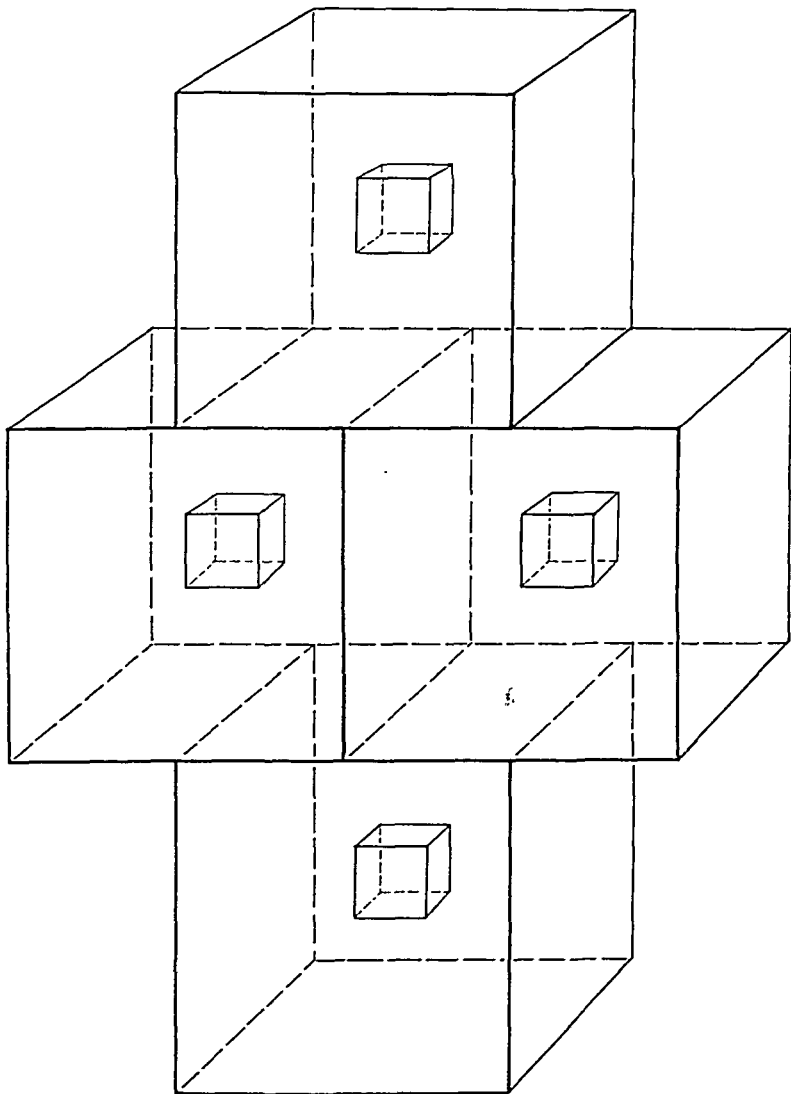


FIG. 2.—Spatial position of cartilage nuclei. (Articular cartilage of calves.)

Metabolism. The metabolism determinations made on surviving slices of bovine articular cartilage were concerned with:

A. Glucolytic Activity or Splitting of Glucose.

B. Oxidative Activity or Oxygen Consumption.

C. Dehydrogenatic Activity or Mobilization of Hydrogen.

A. *Glucolytic Activity.* The ability of articular cartilage to split glucose, as well as other hexoses under both aërobic and anaërobic conditions, was analyzed in 28 experiments. The rate of glucolysis per unit weight of cartilage decreased with progressing age of the animals. When the rate was correlated with the cellular density of the material under analysis it was found that the old cartilage cell was able to split glucose as rapidly as the young cell. In other words, there was no decline of glucolytic activity *per cell* in articular cartilage with advancing age.

Cell respiration is synonymous with oxidation or combustion. The sole function of respiration is to provide energy and hence life for the cell. Impairment of respiration means cell deterioration, and if continued, results in aging or death of the cell.

Respiratory power of a living cell depends upon the orderly action of two main units of the respiratory system:

(a) Dehydrogenatic System: This system mobilizes the hydrogen from various nutrients. It consists of: 1, specific enzymes which combine with the nutrients and activate their hydrogen; and of: 2, specific organic compounds and enzymes which combine with the activated hydrogen and carry it to the—

(b) Oxygen activating system which takes the hydrogen from the carriers and combines it with gaseous oxygen.

(The measurements of the capacities of the Oxygen Activating System are recorded under (B) Oxidative Activity and the capacities of the Dehydrogenatic System are recorded under (C) Dehydrogenatic Activity.)

B. *Oxidative Activity.* The ability and rate of articular cartilage to consume oxygen in the absence of glucose was measured quantitatively in 50 experiments. (The rate of oxygen consumption in the presence of glucose was measured in 20 experiments. The addition of glucose did not increase oxygen consumption but lowered it.)

The rate of oxygen consumption per unit weight of cartilage decreased rapidly with advancing age. In contrast to glucolysis, however, this decrease in respiration proceeded more rapidly than the diminution in cellular density.

Thus, it is seen that under comparable experimental conditions the old cartilage cell consumes less oxygen than the young cartilage cell (*cp.* Fig. 3). This suggests that the respiratory power of the old cartilage cell is diminished.

(C) *Dehydrogenatic Activity.* The ability of the cartilage cell to mobilize hydrogen was determined in 34 experiments by measur-

ing the oxygen uptake of cartilage slices in the presence of methylene blue. This auto-oxidizable redox dye was used as a substitute for the oxygen activating system in the cell in order to estimate the full capacity of the dehydrogenatic system. When the dehydrogenatic activity was correlated with the cellular density, it was apparent that the aging cartilage cell lost but little of its dehydrogenatic power (*cp.* Fig. 3, Hydrogen mobilization).

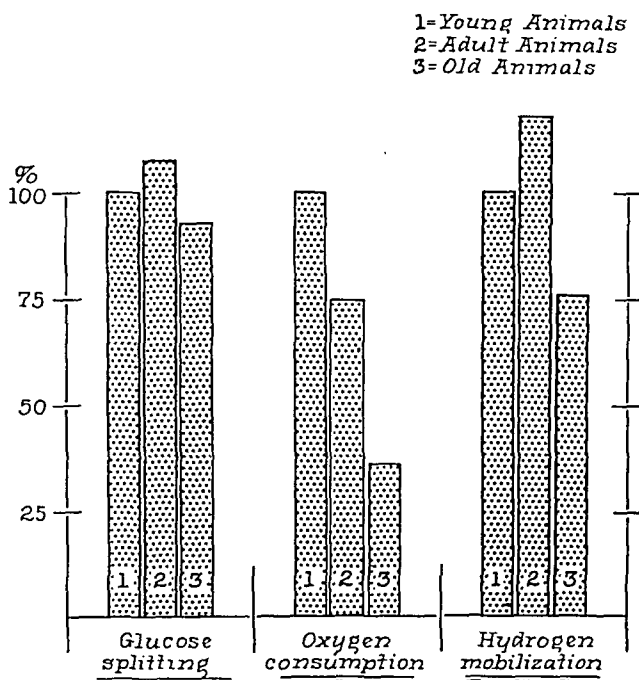


FIG. 3.—Metabolic activity of the cartilage cell.

Summarizing the experiments on respiration it can be stated that:

1. Respiration or oxygen consumption of the articular cartilage cell decreases with age.
2. The rate of respiration decreases more rapidly than can be accounted for by the diminution of the number of cartilage cells which results from aging.
3. The progressive failure of oxygen consumption with age is due to the failure of the oxygen activating system, alone of the three units responsible for cell respiration.

Conclusion and Summary. The joint surfaces of adult cattle may show degenerative changes of the articular cartilage which are typical of hypertrophic arthritis.

Histologic and metabolic studies were made of articular cartilage cells from young, adult and old cattle.

1. Articular cartilage cells diminish in number with advancing age.

2. The nuclei of cartilage cells do not decrease in volume with aging.

3. The ability of the old cartilage cell to split glucose is not less than that of the young cell.

4. The oxygen consumption activity of the old cell is much less than that of the young cell.

5. The declining respiratory rate of the old cartilage cell is due to the failure of the oxygen activating system.

6. It is suggested that the degenerative changes of articular cartilage which accompany aging are related to:

(a) Diminution in number of the cartilage cells incident to age.

(b) Inability of the old cartilage cell to "breathe" adequately.

THE INCIDENCE OF BRUCELLOSIS IN PATIENTS WITH RHEUMATIC DISEASE.

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JOINT and muscle pains may be dominant features of brucellosis.⁷ It is stated¹ that over 50% of patients with brucellosis have rheumatic complaints, which include arthralgia, myalgia, non-suppurative or suppurative arthritis, spondylitis, osteoperiostitis or osteomyelitis. Symptoms referable to the joints were the *chief complaint* in 10% of 67 cases of brucellosis reported by Simpson and Frazier.¹¹ Hardy and his coworkers⁶ found an incidence of arthralgia in 32% of their cases of brucellosis, but evidence of joint inflammation occurred in less than 2%. The incidence and type of joint involvement differs with different strains of the infecting organism. In California where bovine strain of *Brucella* is the predominant type of organism,¹² the incidence and prominence of joint pains was greater than in Iowa where the porcine strain predominated.⁷ However, the bovine strain of *Brucella* causes actual joint inflammation rarely, whereas the porcine strain produces arthritis more commonly but less often than the *melitensis* strain (Hardy). Thus, arthralgia is more common in cases caused by the bovine strain, and joint inflammation, although much less frequent than arthralgia, is usually due to the porcine or *melitensis* strain.

* The Rackham Arthritis Research Unit is supported by the Horace H. Rackham School of Graduate Studies, University of Michigan.

Goldfain^{4a} studied the incidence of brucellosis in patients with rheumatic complaints, most of whom were from rural regions of Oklahoma where milk is rarely pasteurized. Thirty-one of 50 patients were diagnosed as having active brucellosis. The rheumatic diagnosis in these 31 cases were: atrophic arthritis, 9 cases (29%); hypertrophic arthritis, 5; ankylosing spondylitis, 1; chronic fibrositis, 5; psychoneurosis and chronic fibrositis, 2; sciatica, 2. Psychoneurosis alone occurred in 5 cases. The diagnosis of brucellosis was based entirely on laboratory procedures (the skin test, phagocytic index and agglutination reaction) performed and interpreted according to the criteria of Keller, Pharris and Gaub¹⁰ as adapted from Huddleson, Johnson and Hamann⁹ (Table 1).

TABLE 1.—SYSTEM PROPOSED BY HUDDLESON FOR THE DIAGNOSIS OF BRUCELOSIS.

Agglutination test.	Skin test.	Phagocytic power of blood.	Status of patient toward Brucella.
Negative	Negative	0 to 20% of cells, slight	Susceptible
Negative	Positive	0 to 40% of cells, marked	Infected
Positive	Positive	0 to 40% of cells, marked	Infected
Negative	Positive	60 to 100% of cells, marked	Immune
Positive	Positive	60 to 100% of cells, marked	Immune

Later, Goldfain^{4b} reported that, by the same criteria, of 157 patients with rheumatic, neuralgic and/or arthritic symptoms, 80 (51%) had active brucellosis. Twenty-three of these were re-tested after completion of a full course of bacterine therapy and again 3 months later. In the majority of these the skin test became negative or less positive, the leukocytes showed increased phagocytic power and blood agglutinins increased. Twenty-one of the 23 patients became free of symptoms or were improved. It was concluded that recognition and treatment of brucellosis in patients with rheumatic disease favorably influences the course of the rheumatism even though this may not be directly caused by the brucellosis.

These reports of Goldfain suggest that brucellosis is much more frequent in patients with rheumatic disease than is generally considered to be the case. We wondered whether his statistics accurately indicated the prevalence of brucellosis generally throughout this country or whether the high incidence of brucellosis in rheumatic patients might be peculiar to a region in which this disease is rampant. To obtain information regarding the incidence and importance of active brucellosis in patients with rheumatoid arthritis and other types of rheumatic diseases in Michigan the following study was conducted.

Method. Fifty patients who came to the University Hospital with illness characterized by rheumatic symptoms were studied. These were equally divided into two distinctly different groups. The first group consisted of

25 patients with typical atrophic (rheumatoid) arthritis, so diagnosed after careful clinical, laboratory and roentgenographic study. All but 3 in this group had manifestations of activity of the disease. The second group comprised 25 patients with symptoms and manifestations which were not characteristic of any of the common arthritides. Many of these complained of arthralgia or myalgia but demonstrated no joint abnormalities clinically or roentgenographically; others reported that they had had acute joint inflammation which subsided, leaving only arthralgia; still others had hydrarthrosis, or chronic inflammatory joint disease that could not be readily classified; the remainder had periarticular disease (so-called "fibrositis" or "non-articular rheumatism"). The patients in this second group were thoroughly studied—roentgenograms of joints and sedimentation indices were routinely obtained, and when indicated the following studies were performed: systemic roentgenograms, blood cultures, gonococcal complement fixation reactions, electrocardiograms, cytologic examinations and culture of joint fluid, biopsies of muscle and periarticular tissue, sensitization tests and therapeutic tests with salicylates, colchicine, and sulfanilamide or related drugs.

The existence of brucellosis was carefully investigated by both clinical and laboratory means. The anamnesis included inquiry as to the residence, the occurrence of previous unexplained febrile illness or of brucellosis or Bang's disease in the vicinity, the use of raw milk, the raising of cattle, the occurrence of abortion among the cattle, the testing of the cattle for Bang's disease. To allow accurate interpretation of laboratory tests we inquired regarding previous skin tests or vaccine therapy for brucellosis.

The laboratory tests performed were the skin test, agglutination reaction and phagocytic index against *Brucella* and blood culture.^{2,5,8-10} Brucella vaccine was employed for the skin test and the reaction was observed 48 hours after injection. Adopting the criteria of Huddleson, it was considered positive if in addition to an area of erythema there was induration which measured 0.5 cm. or more in diameter. The phagocytic index and rapid slide agglutination tests were performed according to the technique of Gould and Huddleson who consider that by this method a positive test consists of complete agglutination in a titer exceeding 1 to 25. Blood for the serologic tests was obtained prior to the performance of the skin test. In attempts to culture *Brucella*, blood was inoculated into a phosphate buffered beef infusion broth and incubated at 37° C. in an atmosphere of 10% carbon dioxide for 16 days. At 4-day intervals plates of rabbit blood agar were inoculated from the original broth; these were also incubated in a carbon dioxide atmosphere and examined for growth after 24 and 48 hours.

Results. In none of the 25 patients with typical atrophic arthritis were positive results to all three of the diagnostic tests for brucellosis found (Table 2). In 7 cases the phagocytic index was weakly positive but in none of these was there a positive skin reaction. The skin test was positive in 2 patients as the only positive finding. Blood agglutinins for *Brucella* were not obtained in any of the patients in this group. Blood cultures for *Brucella* were performed in 12 cases; all were negative.

Table 3 contains the results in the 25 patients with findings that were not typical of any of the common arthritides. Three of this group had significant blood agglutinins and in addition a positive skin test and positive phagocytic index for *Brucella*. The combination of positive skin test and phagocytic index occurred in 1 instance

and the combination of a positive skin test and positive agglutination test occurred in another. In 4 cases a skin reaction was the only positive laboratory finding. Blood cultures for *Brucella*, performed in 23 cases, were negative.

TABLE 2.—RESULTS OF STUDIES ON PATIENTS WITH TYPICAL ATROPHIC ARTHRITIS.

Case.	Residence.	Raised cattle.	Cattle tested for Bang's disease.	Occurrence of abortions among cattle.	Used raw milk.	Previous skin tests or vaccine therapy in patients.	Activity of arthritis.	<i>Brucella</i> agglutination test.	Brucellergin skin test.	Phagocytic index for <i>Brucella</i> .	Blood culture for <i>Brucella</i> .
1	Rural	Yes	No	No	Yes	None	Inactive	Neg.	Neg.	Neg.	Neg.
2	Rural	Yes	No	No	Yes	Both	Active	Neg.	Neg.	Neg.	Neg.
3	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
4	Rural	Yes	No	Yes	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
5	Urban	No	No	None	Active	Neg.	Neg.	50% None 46% Slight 4% Moderate	Neg.
6	Urban	No	No	None	Active	Neg.	Neg.	24% None 64% Slight 12% Marked	Neg.
7	Rural	Yes	Yes	No	Yes	None	Active	Neg.	Neg.	16% None 74% Slight 10% Moderate	Neg.
8	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	12% None 70% Slight 18% Moderate	Neg.
9	Rural	Yes	Yes	No	Yes	None	Inactive	Neg.	Neg.	Neg.	Neg.
10	Urban	No	Yes	No	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
11	Urban	No	No	None	Active	Neg.	Neg.	Neg.	Neg.
12	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
13	Urban	No	No	None	Active	Neg.	Neg.	90% None 10% Slight 96% None 4% Slight	Neg.
14	Urban	Yes	?	?	Yes	None	Active	Neg.	Neg.	96% None 4% Slight	Neg.
15	Rural	Yes	Yes	No	Yes	None	Inactive	Neg.	Pos.	Neg.	Neg.
16	Urban	No	Yes	No	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
17	Urban	No	No	None	Active	Neg.	Neg.	Neg.	Neg.
18	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
19	Urban	No	No	None	Active	Neg.	Neg.	Neg.	Neg.
20	Rural	Yes	Yes	No	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
21	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
22	Rural	Yes	Yes	No	Yes	None	Active	Neg.	Pos.	Neg.	Neg.
23	Urban	No	No	None	Active	Neg.	Neg.	Neg.	Neg.
24	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
25	Urban	No	No	None	Active	Neg.	Neg.	76% None 20% Slight 4% Moderate	Neg.

Discussion. To obtain precise data as to incidence of a disease it is necessary to have indisputable diagnostic tests. Unless the organisms are isolated, the existence of brucellosis cannot be proven. It is generally agreed that the laboratory tests for brucellosis are often confusing, may even be misleading and allow for different interpretation. The agglutination test is the most reliable of the common diagnostic procedures, but it is not infallible. Evans³ found a negative agglutination test (titer less than 1 to 40 by the tube method) in 46% of patients with chronic brucellosis. Other authors report absence of agglutinins in 5% to 15% of the cases. Opinions differ as to the minimum titer that is diagnostically significant. Furthermore, there are sources of possible error in inter-

pretation because the titer may remain high after recovery from the disease or agglutinins may develop in individuals exposed to infection although they have never been ill.

The brucellergen skin test is less reliable than the agglutination test because it is less specific. In Evans' series a positive skin test occurred only four times as frequently in patients with chronic brucellosis as in patients ill with other diseases. Three explanations have been advanced for the occurrence of a positive skin test in the absence of active brucellosis. Repeated contacts with *Brucella* incident to handling infected animals or drinking infected milk may produce a state of hypersensitiveness as manifested by skin reaction to *Brucella* antigens although symptoms of disease have never been present. Secondly, the allergic state may persist for years after complete recovery from the disease. Thirdly, "false positive" brucellergen tests do occur, possibly on the basis of general bacterial hypersensitivity. Evans and her associates found a positive skin test in 13.7% of 321 patients ill with diseases other than brucellosis and in 10.7% of healthy subjects.

The phagocytic index is the least reliable of the diagnostic test because it is the least specific. This test was found by Evans to be positive in 30.7% of patients ill with chronic diseases other than brucellosis. Huddleson, Keller and others believe that the degree of the phagocytic activity indicates the patient's status in regard to the infection (susceptible, actively diseased or immune). Evans and her associates do not agree inasmuch as they found no consistent correlation between the phagocytic power of the leukocytes and the state of the infection. Our experience with this test is in accord with Evans. Positive phagocytic and skin tests add weight to the evidence given by a positive agglutination reaction. In Evans' series the combination of all three positive reactions occurred ten times as frequently in chronic brucellosis as in patients ill with other diseases. However, brucellosis, proved by recovery of the organism, may occur even though all three tests give negative results.³

Since recovery of *Brucella* by culture or by animal inoculation can be accomplished in only a small percentage of the cases, requiring this for establishment of the diagnosis would result in not diagnosing the disease in many instances. In our cases no positive blood cultures were obtained so that the diagnosis of brucellosis is not unequivocal. We considered the disease to exist when the history, clinical findings, specific laboratory tests for brucellosis and the exclusion of other disease indicated that chronic brucellosis was the most likely diagnosis. The diagnosis of *possible* chronic brucellosis was made if the above-mentioned evidence was less convincing.

We feel that brucellosis did not exist in any of the patients with typical atrophic arthritis (Group 1). In none were the history, symptomatology and physical findings suggestive of, or the

TABLE 3.—RESULTS OF STUDIES ON PATIENTS WITH RHEUMATIC SYMPTOMS AND MANIFESTATIONS NOT CHARACTERISTIC OF ANY OF THE COMMON ARTHRITIDES.

Case.	Residence.	Raised cattle.	Cattle tested for Bang's disease.	Occurrence of abortions among cattle.	Used raw milk.	Previous skin tests or vaccine therapy in patients.	Fever.	Rheumatic symptoms.	Physical signs of joint disease.	Brucella agglutination test.	Brucellergen skin test.	Phagocytic index for Brucella.	Blood culture for Brucella.	Final diagnosis.
1	Urban	No	No	No	Yes	Transient red, swollen joints; muscle soreness	Transient acute joint inflammation; muscle tenderness	Neg.	Neg.	Neg.	Neg.	Angiodermatomyositis; acute lupus erythematosus disseminatus
2	Rural	Yes	Yes	No	Yes	No	No	Swelling of left knee every 9 days	Hydrarthrosis without bony at necromality	(2) Neg.	..	76% None 24% Slight	Neg.	Intermittent hydrarthrosis; ovalbumin sensitivity
3	Urban	No	No	No	No	Aches in neck, shoulders, arms and legs	None	Neg.	Pos.	14% Moderate 86% Marked	Neg.	Psychoneurosis
4	Rural	Yes	No	No	Yes	No	Yes	Arthralgia and myalgia, legs and knees	None	Pos. 1:100	Pos.	2% None 2% Slight 6% Moderate 90% Marked	..	Chronic brucellosis
5	Urban	No	No	Yes	Yes	No	Yes	Arthralgia and myalgia, legs and arms	None	Pos. 1:80	Pos.	Neg.	Neg.	Possible chronic brucellosis
6	Rural	Yes	No	Yes	Yes	No	Yes	Arthralgia, knees and ankles	None	Pos. 1:50	Pos.	22% None 15% Slight 17% Moderate 46% Marked	Neg.	Chronic brucellosis
7	Urban	No	No	No	Yes	Painful, stiff shoulders, knees and wrists	Hydrarthrosis both knees; limitation in motion both wrists	Neg.	Neg.	Neg.	Neg.	Atypical atrophic arthritis
8	Rural	Yes	?	?	Yes	No	Yes	Painful, swollen right knee and heels	Acute joint inflammation, right knee; Achilles' bursitis	Neg.	Neg.	Neg.	Neg.	Gonococcal arthritis and bursitis
9	Urban	Yes	Yes	No	Yes	No	No	Severe arthralgia of elbows, knees and shoulders	None	Pos. 1:200	Pos.	100% Marked	Neg.	Chronic brucellosis
10	Rural	Yes	Yes	No	Yes	No	Yes	Arthralgia, both knees	None	Neg.	Pos.	Neg.	Neg.	Possible chronic brucellosis
11	Rural	Yes	No	Yes	Yes	No	Yes	Arthralgia and myalgia, both arms	None	Neg.	Pos.	Neg.	(2) Neg.	Possible chronic brucellosis

12	Rural	Yes	No	Yes	No	Yes	No	Yes	No	Pain and stiffness of fingers and shoulders	Limitation of motion of shoulders and finger joints with puckering of the subcutaneous tissue of the palms	Neg.	Neg.	Neg.	Fibrositis
13	Urban	No	..	No	..	No	..	No	..	Painful swelling of all joints	Acute inflammatory changes of the joints	Neg.	Neg.	Felty's syndrome with superimposed hemolytic streptococcus septicemia
14	Rural	Yes	Yes	No	Yes	No	Yes	No	Yes	Painful, stiff shoulders and fingers	Periarthritis of shoulders; tenderness and swelling of metacarpophalangeal joints and proximal phalangeal joints	Neg.	Neg.	Neg.	Periarthritis of shoulders; atrophic arthritis of hands
15	Urban	No	..	No	..	No	..	No	..	Myalgia of lower extremities, shoulders and forearms	Muscle tenderness	Neg.	Neg.	Neg.	?Muscular rheumatism
16	Urban	No	..	No	..	No	..	No	..	Low back pain; arthralgia of shoulders, neck, feet, left knee and wrist	Fusiform swelling and stiffness of proximal phalangeal joints of right index finger	Neg.	Neg.	(2) Neg.	Atrophic arthritis
17	Rural	Yes	No	No	Yes	No	Yes	No	Yes	Severe arthralgia shoulders, hands and knees	None	Neg.	Neg.	Neg.	Undiagnosed
18	Rural	Yes	No	Yes	Yes	No	Yes	No	Yes	Swollen wrists; soreness of shoulders, neck, hip, knees and feet	Acute inflammatory changes of both wrists and all metatarsophalangeal joints	(3) Neg.	Neg.	(2) Neg.	Atypical atrophic arthritis
19	Urban	No	..	No	..	No	..	No	..	Swelling of right knee	Hydrarthrosis	Neg.	Neg.	Neg.	Hydrarthrosis, ?etiology
20	Rural	Yes	No	Yes	No	No	Yes	No	Yes	Arthralgia, arms and shoulders; pain and swelling of both ankles	Pes planus	Neg.	Neg.	Neg.	Possible chronic brucellosis
21	Rural	Yes	No	No	Yes	No	Yes	No	Yes	Arthralgia, elbows and knees	None	Neg.	Neg.	Neg.	?Rheumatic fever
22	Urban	No	..	No	..	No	..	No	..	Swelling of knees, ankles, shoulders, wrists and elbows	Hydrarthrosis, both knees	Neg.	Neg.	Neg.	Atypical atrophic arthritis
23	Rural	Yes	No	Yes	Yes	No	Yes	No	Yes	Arthralgia and myalgia, arms and legs	None	7% None 30% Slight 63% Moderate	Neg.	Neg.	?Psychoneurosis; possible chronic brucellosis
24	Urban	No	..	No	..	No	..	No	..	Painful swelling of knees, ankles, wrists and elbows	None	Neg.	Neg.	Neg.	?Malingering
25	Rural	Yes	No	No	Yes	No	Yes	No	Yes	Arthralgia and myalgia of legs	None	Neg.	Neg.	Neg.	Possible chronic brucellosis

laboratory studies diagnostic of, brucellosis. The finding of phagocytic power toward *Brucella* in 28% of this group was to be expected since Evans found a positive phagocytic reaction in 30.7% of patients with chronic diseases other than brucellosis. In the absence of other evidence for brucellosis, we interpret a positive phagocytic test as a "false positive" and not diagnostic of active brucellosis. The two skin reactions occurred in farmers who had cattle on their farms and who used raw milk. The history, physical examination and other laboratory tests failed to yield further evidence for active brucellosis. Since Evans found a positive skin test in 13.7% of patients ill with diseases other than brucellosis and in 10.7% of healthy subjects, the occurrence of two skin reactions in our 25 cases (8%) is not surprising.

In our second group of patients the diagnosis of chronic brucellosis was made in 3 instances and "possible chronic brucellosis" was diagnosed in 6 cases. All 3 of the patients diagnosed as chronic brucellosis had drunk unpasteurized milk. Two had low-grade fever, one (Case 9) was afebrile. All gave positive results to the three diagnostic tests. In 2 (Cases 4 and 9) the leukocytes showed marked phagocytic activity to the extent that according to Huddleson's criteria they would have been classified as "cured." Yet, they exhibited manifestations of active disease. All complained of *arthralgia* but exhibited no joint abnormalities. One (Case 6) stated that at the onset of his illness his knees and ankles were swollen and red; these changes disappeared and he had only *arthralgia* when he entered the hospital. Case 4 was treated with repeated courses of sulfanilamide therapy without any appreciable benefit. Case 6 was given sulfanilamide and *Brucellin* vaccine (Parke-Davis) and was afebrile and free of symptoms when discharged. Case 9 was treated with sulfanilamide and during this therapy fever was produced by intravenous injection of typhoid antigen three times. There was marked improvement. He had been bed-ridden because of severe *arthralgia*; at the time of discharge he was ambulatory, and complained of only minimal aching in the right shoulder and elbow.

In the group of 6 patients with "possible chronic brucellosis" a definite diagnosis would have been made in at least 3 instances if less rigid criteria were employed. Case 5 used raw milk from infected cows and had positive agglutination and skin tests for *Brucella*. She also had non-specific bronchitis. Whether brucellosis or bronchitis accounted for her symptoms is not clear. The positive laboratory tests could have been due to brucellosis in the past. Sulfapyridine therapy resulted in a complete cure. Case 11 was diagnosed brucellosis 6 years before we saw him because a positive agglutination test was found after he drank raw milk. During our study a skin reaction was the only positive test. He was given sulfanilamide without any effect. Case 20 complained of mild

arthralgia of the joints of the upper extremities, painful, swollen feet and low-grade fever. He had consumed raw milk. He had pes planus and foot strain which could have accounted for his foot complaints; other symptoms were minimal and no treatment for brucellosis was administered. Positive skin tests were observed in Case 10 who had a duodenal ulcer and Case 25 who had pernicious anemia in remission. Their joint difficulties and occasional mild temperature elevations were considered insufficient to warrant treatment for possible brucellosis. Case 23 complained of asthenia, constipation, arthralgia and myalgia of the extremities, and had low-grade fever. He used raw milk and abortion had occurred among his cows. All the tests for brucellosis yielded negative results.

Thus, by our criteria, none of the 25 patients with characteristic atrophic arthritis had active brucellosis. Of the 25 patients in Group 2, those with miscellaneous rheumatic disorders, 3 (12%) were diagnosed active brucellosis and 6 (24%) were diagnosed as "possible brucellosis"—a total of 36% of a group who might have had undulant fever. Of all 50 cases (Groups 1 and 2), the incidence of brucellosis was 18% (including the 6 cases with "possible brucellosis").

To satisfactorily contrast our findings with the reports of Goldfain, it is necessary to analyze our cases by the criteria he used which depend entirely on the laboratory tests (Table 1). By these criteria 2 of our patients with atrophic arthritis would be diagnosed as active brucellosis, an incidence of 8%. This incidence is far less than 46% which occurred in Goldfain's cases of atrophic arthritis. Six cases (24%) of our Group 2 would by his method be diagnosed as active brucellosis. Thus, a total of 8 cases (16%) of our 50 patients had brucellosis by the criteria of Goldfain, in contrast to 62% of 50 patients reported by him! Many of our patients were farmers and used unpasteurized milk, comparable in these respects to the patients studied by Goldfain. These findings show quite clearly that the incidence of brucellosis in patients coming to the hospital complaining primarily of rheumatic symptoms is decidedly less in Michigan than in Oklahoma, most likely because the prevalence of this disease is less in Michigan than in Oklahoma.

Thus, the importance of brucellosis in regard to rheumatic disorders is far less in Michigan and probably most parts of the United States than the reports of Goldfain suggest. Arthralgia and other rheumatic *symptoms* are, to be sure, frequently observed in brucellosis, and that disease should be suspected especially in febrile patients with rheumatic complaints. However, joint inflammation was not observed in any of our patients who had brucellosis, or even "possible brucellosis." It seems quite clear, therefore, that brucellosis is seldom, if ever, the cause of chronic non-suppurative polyarthritis.

Conclusions. The incidence of brucellosis was studied in 25 patients with characteristic atrophic arthritis and in 25 cases of other

rheumatic disorders. None of the first group had evidence which, by our criteria, was diagnostic of brucellosis. Of the second group, 3 (12%) had quite convincing evidence of active brucellosis, and 6 others had "possible brucellosis." The incidence of brucellosis in rheumatic patients is, therefore, much less in Michigan and probably most parts of the United States than is reported from Oklahoma.

Arthralgia and other rheumatic symptoms are common in brucellosis and *temporary*, non-purulent joint inflammation may occur. Our data indicate that brucellosis is seldom, if ever, a cause of *chronic* non-purulent joint inflammation.

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INCIDENCE OF PULMONARY TUBERCULOSIS IN SCHIZOPHRENIC PATIENTS FOLLOWING METRAZOL CONVULSIVE THERAPY.

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THE treatment of functional psychoses with metrazol convulsive therapy is used extensively in many hospitals. Although numerous reports have been published dealing with dangers of this treatment, such as vertebral fractures and lung abscesses, comparatively little emphasis has been laid upon a possible complication in the form of pulmonary tuberculosis. That schizophrenic patients, who have been in institutions for many years, develop tuberculous lesions is not a new observation. However, the incidence of tuberculosis appeared to be much higher in our patients after treatment with metrazol. This was especially noted in our autopsy material, since in 6 out of 7 patients a severe tuberculous involvement of the lungs was observed.

Already von Meduna and Friedman^{3,5} have mentioned 1 patient who died of acute pulmonary tuberculosis following metrazol treatment. Kraus² reported 1 patient out of 64 cases treated with metrazol, who did not present Roentgen ray findings 9 months previous to the treatment, but developed an acute tuberculous pneumonia after 6 injections of metrazol. van de Graaff⁶ *et al.* also reported 4 cases of tuberculous pneumonia following treatment. They considered the possibility that cardiazol injections might have activated a latent pulmonary tuberculosis. Demay¹ *et al.* reported 3 cases of schizophrenia with manifestations of pulmonary tuberculosis after metrazol therapy. Recently, in a comprehensive survey of the consequences of metrazol, Read⁴ stressed the occurrence of pulmonary tuberculosis following metrazol treatment.

To obtain more objective data on the relationship between metrazol therapy and the incidence of tuberculosis, all coöperative schizophrenic patients (277 in all) who had been previously treated with metrazol, as well as a comparable non-treated group, were carefully reëxamined. These examinations consisted of a careful physical examination and fluoroscopic studies. In those with doubtful findings, Roentgen ray films were taken. In this way 25 schizophrenic patients (18 men and 7 women) were found to have tuberculous lesions which had developed either during or following the course of metrazol treatment. None of these patients presented clinical signs of pulmonary tuberculosis before the therapy was instituted, though the amount of latent tuberculosis present could not be estimated from the evidence available. Most of them had been in the hospital for some time, and in only 1 patient was the hospitalization period of short duration (4 months). The average period of hospitalization was 47 months prior to metrazol treatment. The percentage of active cases of tuberculosis was 8.3 in the group treated with metrazol over a period of 3 years, which is considerably higher than that of tuberculosis in the rest of our schizophrenic patients (3%) during the same period of 3 years. The higher percentage is even more significant since patients who were considered poor risks were rarely treated with metrazol.

Most of the patients who developed tuberculosis were in the age group of 20 to 29 years (Table 1). However, it is striking that those who developed tuberculosis *immediately* following metrazol treatment were considerably older than the rest of the group. Four were over 40 and 2 over 30 years of age. Thus, it seems that the pulmonary status of patients over 40 should be carefully studied before institution of this therapy.

The amount of metrazol and the number of convulsions present no direct relationship to the development of tuberculosis or the severity of the lesion (Table 1).

The onset of the tuberculous process in many of these patients was not only acute, but also dramatic. In some patients the infec-

tion was so overwhelming as to simulate clinically a picture of lobar pneumonia with high temperature, respiratory distress and local physical findings. In 2, the tuberculous process started with a pleurisy with effusion. In 3, the metrazol treatment had to be interrupted because of development of pulmonary tuberculosis, while in the remainder a varying period of time intervened before the tuberculous process was discovered. It is very difficult to detect clinically small and even large tuberculous lesions in uncooperative psychotic patients. Although all our chronic patients have a complete physical examination at 6-month intervals, 5 patients who had no clinical findings of tuberculosis when this study was started and who had not been suspected, were discovered on the fluoroscopic survey to have *early* pulmonary tuberculosis (see Table 1). This finding emphasizes the importance of routine pulmonary fluoroscopy in a mental hospital, especially for those patients who receive convulsive therapy.

The course of the tuberculous process in many of our patients was acute and progressive; 9 died, 4 of them within 4 months after the first appearance of the infection. Five illustrative case histories follow, indicating the course of events in several of those patients with acute onset. Tubercle bacilli were demonstrated in the sputum or by guinea-pig inoculation in all patients.

Case Abstracts. CASE 1.—E. D., female, 43 years of age, admitted October 19, 1928, diagnosed hebephrenic dementia precox. Mental symptoms began in 1925, at the age of 30 with untidiness in habits and levelling of emotion. On admission she was extremely indifferent, out of contact, and actively hallucinated. For the past 10 years, her mental condition has been stationary. Metrazol therapy started on August 29, 1938. Three weeks later, the day after her ninth convulsion, she became acutely ill, developed a temperature of 104°, and dullness over the entire left lung with occasional crepitant râles. Temperature dropped the next morning to 100.2°. Roentgen ray taken a few days later revealed a large cavity below the fourth rib anteriorly in the left lung with soft exudative infiltration about it. The patient continued to have a septic fever with progressive tuberculosis and expired on October 8, 1938.

CASE 2.—B. L., female, 33 years of age, admitted December 15, 1933, diagnosed catatonic dementia precox. She had been ill for many years, was manneristic, impulsive, had bizarre ideas, and attitudinized. Here, she actively hallucinated, attitudinized and was impulsive. Started on metrazol therapy on January 10, 1938, receiving 20 treatments with 15 convulsions with marked mental improvement. On March 25, 1938, she relapsed mentally and received 3 more treatments. The day after the last convulsion she became acutely ill with a temperature of 104.6°. Roentgen ray revealed left pleurisy with effusion. Patient was treated on the tuberculosis service until July 31, 1939, when she was discharged arrested.

CASE 3.—E. R., male, 23 years of age, admitted July 24, 1936, diagnosed undetermined dementia precox. Five weeks before admission a change of personality was noted, when he became depressed and began to act peculiarly. Roentgen ray taken July 27, 1936, was negative for pulmonary tuberculosis. He became a feeding problem and on December 6, 1937, was started on metrazol therapy, receiving nine shocks. On December 29, 1937, 2 days after his last convulsion, he became acutely ill with a tempera-

ture of 105° and physical findings suggestive of tuberculous pneumonia. Roentgen ray on January 3, 1938 (4 days later) showed a marked area of infiltration 8 cm. in diameter in the middle zones of the right lung. On March 15, 1938, a right tuberculous pleurisy with effusion developed. The patient was paroled improved on June 12, 1938, with active tuberculosis, and transferred to a tuberculosis sanitarium.

CASE 4.—E. N., male, 23 years of age, admitted April 3, 1936, diagnosed hebephrenic dementia precox. There was a gradual onset of the psychosis with bizarre ideas and untidy habits. On May 27, 1937, he was started on metrazol therapy and received 23 convulsive treatments. On August 31, 1937, 4 days after the last convulsion, a tuberculous pleurisy with effusion developed. Patient remained on the tuberculous service until his death on November 20, 1939, from progressive pulmonary tuberculosis.

CASE 5.—L. T., female, 43 years of age, admitted October 16, 1937, diagnosed hebephrenic dementia precox. She had been mentally ill since 1927, with carelessness about her personal appearance, uncoöperativeness, hallucinations, and impulsive behavior. On February 3, 1938, metrazol therapy was started. On April 12, 1938, 12 days after her seventeenth convulsion, a pneumonic process developed in the right upper lobe with a temperature of 103°. Roentgen ray showed moderately advanced tuberculosis. Her pulmonary condition did not improve with bed rest, and on August 9, 1938, she was started on artificial pneumothorax. On August 11, 1939, she was discharged from the tuberculous service as an arrested case with mental condition unchanged.

TABLE 1.—PULMONARY TUBERCULOSIS AFTER METRAZOL CONVULSIONS

Patient.	Sex.	Age.	Metrazol.		Pulmonary tuberculosis.			
			Con- vulsion.	Grams.	Occurrence after last convulsion.	Type of onset.	Degree of in- volvement on Roentgen ray.	Course.
1 E. D.	F	42	9	4.4	1 day	Acute	Far advanced	Death
2 B. L.	F	33	17	13.8	1 "	Acute	Pleural eff.	Arrested
3 E. R.	M	23	9	8.7	2 days	Acute	Mod. adv.	Arrested
4 E. N.	M	23	23	18.4	4 "	Acute	Far adv.	Death
5 L. T.	F	43	16	8.8	12 "	Acute	Mod. adv.	Arrested
6 W. L.	M	40	29	28.8	14 "	Acute	Mod. adv.	Death
7 H. J.	M	30	15	8.7	24 "	Acute	Pleural eff.	Arrested
8 L. R.	M	26	25	16.3	49 "	Fluoro.	Minimal	Arrested
9 E. G.	F	41	10	4.0	16 wks.	Acute	Far adv.	Death
10 A. D.	F	26	28	13.6	5 mos.	Chronic	Far adv.	Death
11 O. Q.	M	18	50	45.8	8 "	Chronic	Far adv.	Death
12 O. H.	M	24	15—	10.6	9 "	Fluoro.	Minimal	Active
13 M. K.	F	32	15	9.4	10 "	Chronic	Mod. adv.	Active
14 H. F.	M	21	26	24.3	11 "	Chronic	Minimal	Arrested
15 E. S.	M	34	2	1.5	12 "	Chronic	Mod. adv.	Active
16 S. R.	F	25	10	6.4	13 "	Chronic	Minimal	Arrested
17 J. E.	M	27	25	17.9	14 "	Chronic	Minimal	Active
18 E. T.	M	29	15	12.0	15 "	Chronic	Minimal	Active
19 W. G.	M	18	25	24.9	16 "	Chronic	Mod. adv.	Death
20 J. K.	M	37	43	50.3	16 "	Chronic	Far adv.	Death
21 A. T.	M	26	11	8.2	17 "	Chronic	Far adv.	Death
22 W. A.	M	39	60	49.8	18 "	Chronic	Mod. adv.	Arrested
23 F. R.	M	24	25	16.0	22 "	Fluoro.	Minimal	Arrested
24 J. P.	M	45	42	23.0	25 "	Fluoro.	Minimal	Active
25 A. F.	M	27	25	18.0	25 "	Fluoro.	Minimal	Active

Comment. The data presented in Table 1 show that metrazol convulsive therapy has caused a considerable increase in the incidence of pulmonary tuberculosis in the Elgin State Hospital. This increase is even more pronounced if one considers the fact that the patients treated with metrazol were carefully selected, and those

having known tuberculosis were rejected. Whether the activation of the latent tuberculous process is due to mechanical factors causing a rupture of a walled-off focus, or whether allergic, circulatory, or toxic changes occur in the lung, can only be decided experimentally. As was observed from our material, the pulmonary lesion is usually an extensive exudative infiltration of pneumonic consolidation, often bilateral, which shows a marked tendency to progress unfavorably. Pleurisy with effusion occurs very early following treatment, but in our 2 cases was easily arrested. The importance of carefully reexamining metrazol treated patients for pulmonary tuberculosis whether or not respiratory tract symptoms develop or an elevation in temperature occurs cannot be emphasized too strongly.

In psychiatric practice the question may arise whether one should treat the psychotic behavior even in the presence of active pulmonary tuberculosis. A very excited patient who refuses to eat and who regurgitates tube feedings and is rapidly failing physically may be in great danger if treated conservatively. Often in this type of patient metrazol will produce a rapid interruption of the psychotic picture. One of our patients was treated under such circumstances. She was rapidly failing physically, had active pulmonary tuberculosis, was resistive and uncoöperative, and regurgitated her tube feedings. However, her psychotic symptoms were of recent onset, her prepsychotic personality was good, and a careful evaluation of the psychosis pointed to a very good prognosis providing she did not die of her pulmonary tuberculosis. Accordingly, she received metrazol therapy with complete mental recovery. Her tuberculosis showed steady improvement throughout the period of treatment and later became completely arrested.

Conclusions. 1. Twenty-five (8.3%) patients with schizophrenia treated with metrazol convulsive therapy, developed pulmonary tuberculosis as compared with 3% of the schizophrenics not so treated.

2. In 9 of these the onset was acute, occurring during treatment or within 4 months of the institution of metrazol therapy. We believe most of these to be due directly to the metrazol therapy.

3. Metrazol should be given in the presence of active pulmonary tuberculosis only when all the risks have been considered and when the mental condition is very seriously influencing the physical status of the individual.

4. Careful pulmonary examination including Roentgen ray or fluoroscopic study is indicated before the institution of therapy.

5. All patients should be fluoroscoped at 3-month intervals following therapy for at least 2 years.

We wish to thank Dr. Charles F. Read, Managing Officer, for his helpful suggestions and encouragement in the completion of this study.

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A NEW METHOD FOR STUDY OF THE FASTING INSULIN REQUIREMENT OF THE SEVERE DIABETIC.

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CONTROL of the severe diabetic continues as a major problem in insulin therapy, and plans or methods by which such patients may be successfully managed are definitely needed. Much of the difficulty in the management of these patients depends upon the fact that they require insulin not only to cover their dietary intake, but also in the period during which food is not being absorbed. This postabsorptive period occurs principally at night, with the usual dietary schedule. The amount of insulin necessary to prevent this rise of the blood sugar in the postabsorptive state is defined as the basal insulin requirement.^{2a} Both of these insulin needs must be met to control the severe diabetic satisfactorily. Actual studies^{4,5} indicate that two different types of insulin are required: one with a quick, strong action, suitable for covering carbohydrate absorption from the diet, properties of regular insulin, and the other with a slow prolonged action and ability to influence carbohydrate metabolism slowly, suitable for controlling the basal requirement during the night, without danger of hypoglycemia, properties of protamine zinc insulin.

A practical plan for the selection of diabetic patients who have a basal insulin need, and a clinical method by which this requirement may be measured are presented in this paper.

Patients from the Diabetic Service of the Los Angeles County General Hospital were used for this study of basal insulin requirement. All were uncomplicated diabetics who had been in the hospital for several weeks. Protamine zinc insulin, if used, was discontinued 36 to 48 hours before tests were made. During the 14 hours immediately preceding the tests and during the period in which they were made, the patients received no food. Blood sugar

determinations were done on oxalated venous blood by the Folin-Wu micro-method, except those done during the fasting period which were done by the Benedict method. U10 regular insulin, measured with a 0.25 cc. syringe, was used for the basal insulin determination to insure accurate measurement of the small doses.

The diabetics studied were easily separated into two groups by the results of blood sugar determinations made during a fasting period which extended from 7 A.M. to 1 P.M. The basal insulin requirement of severe diabetics is clearly indicated by a rise of the blood sugar during the fasting state (Table 1) even with regular

TABLE 1.—BLOOD SUGAR CONCENTRATIONS* OF FASTING SEVERE DIABETICS.
(Patients fasting 14 hours before and during test.)

Time.	J.D., 660-551 Male 56.	F.T., 706-586 Female 14.	F.B., 698-247 Female 13.	W.D., 233-944 Male 33.	B.P., 629-381 Female 15.	E.T., 660-461 Male 14.
Midnight .	No insulin	10 units†	20 units†	5 units†	25 units†	No insulin
A.M. . .	202	100	70	58	260	136
8 A.M.	169	303	...
9 A.M. .	241	198	241	130	345	222
10 A.M.	200	323	...
11 A.M. .	290	206	267	208	400	185
Noon	204	435	...
1 P.M. .	323	...	303	252	...	182

* Milligrams per 100 cc.

† Regular insulin.

insulin at midnight. Individual rises varied from 44 to 233 mg. in 6 hours. In contrast to this the curves which resulted from determinations of the blood sugar in mild diabetics who were fasting and had no insulin at midnight, were flat, and indicated no basal insulin requirement (Table 2). This is a simple method for determining which patients have a basal insulin requirement.

TABLE 2.—BLOOD SUGAR CONCENTRATIONS* OF FASTING MILD DIABETICS.
(Patients fasting for 14 hours before and during test.)

Time.	F.F., 663-516, Male 32.	G.B., 645-568, Female 24.	M.B., 390-488, Female 33.	M.H., 712-574, Female 32.
Midnight	155
3 A.M.	174
7 A.M.	118	116	105	167
9 A.M.	103	152	100	174
11 A.M.	91	149	87	167
1 P.M.	86	132	94	174

* Milligrams per 100 cc.

Others^{6,7} have recognized the fact that the blood sugar of the severe diabetic rises during the fasting state, and particularly at night. The therapeutic importance of this rise, however, has not been emphasized and few quantitative determinations of the requirement have been made.^{1,4}

Quantitative measurement of the basal insulin requirement of 7 patients, who were found to have a rise of blood sugar during the fasting state, were made. The results in 4 of these patients are summarized in Tables 3 to 6. A detailed analysis of one record (B.P. 629-381, Table 3, Sect. 2), will illustrate the method used:

TABLE 3.—PATIENT B.P., 629-381, WHITE FEMALE, AGE 15.
(Patient fasting for 14 hours before and during each test.)

SECTION 1.			SECTION 2.			SECTION 3.			SECTION 4.		
Blood sugars fasting.			Basal insulin determination subcut.* regular insulin.			Basal insulin determination I.V.† regular insulin.			Basal insulin determination with one dose PZI.‡		
4-10-40.	Bl. sug., mg. per 100 cc.	Reg. insulin.	4-19-40.	Bl. sug., mg. per 100 cc.	Reg. insulin.	4-23-40.	Bl. sug., mg. per 100 cc.	Reg. insulin, I.V.	5-7-40.	Bl. sug., mg. per 100 cc.	PZI.
Midnight ..	25		Midnight ..	30		Midnight ..	30		Midnight..	30 (subc.)*	R.I.
7 A.M.	260		7:08 A.M.	148.1		7:30 A.M.	156.2	(subc.)	7:15 A.M.	98	
8	303		7:10	..	2½	8:00	..	4	7:16	..	20 PZI
9	345		8:08	175.4		8:28	163.9		9:30	95.2	
10	323		8:10	..	2½	9:01	..	2	11:30	114.9	
11	400		8:43	170.9		9:27	137.0		1:40 P.M.	163.9	
12	435		9:10	..	2½	10:00	..	2	3:20§	175	
			9:40	190		10:28	120.5				
			10:09	..	3	10:58	..	2			
			10:35	190		11:27	111.1		7:00 A.M. to 3:20 P.M.—		
			11:08	..	3	11:59	..	2	6.75 gm. sugar in urine.		
			11:34	190		12:27 P.M.	106.4				
			12:14 P.M.	..	3	1:00	..	2			
			12:40	150		1:27	104.2				
			1:20	111		2:00	..	2			
						2:26	86.2				
			6 A.M. to 1:30 P.M.—7.6			7:30 A.M. to 2:30 P.M.—no					
			gm. sugar in urine.			sugar in urine.					

* Subcut. = subcutaneously in all tables.

† I.V. = intravenous in all tables.

‡ PZI = protamine zinc in all tables.

§ This does not represent end of PZI activity, although test was stopped at this point.

1. *Preparation for Test:* (a). The patient received no food for 14 hours before starting the test, nor during the test.

(b). Thirty units of regular insulin were given at midnight before the test to insure a blood sugar within the normal range at the start of the test. The amount of insulin required at midnight varies with the severity of the case, and the previous level of control. The least severe diabetics require 5 to 10 units, the most severe 25 to 30 units.

2. *The Test:* (a). Regular insulin was given subcutaneously at hourly intervals and blood sugar determinations were made at hourly or half-hourly intervals.

(b). The insulin dosage was changed as indicated by a rising or falling level of the blood sugar. As the blood sugar rose from 148.1 to 190 mg. per 100 cc. from 7:08 A.M. to 9:40 A.M. with the use of 2½ units per hour, the amount was increased to 3 units per hour. This

(Patient fasting for 14 hours before and during each test.)

* Subcutaneously.

(Patient fasting 14 hours before and during each test.)

* Subcutaneously.

amount was too great as the blood sugar fell from 190 to 111 mg. per 100 cc. between 4½ and 6 hours. Part of this fall, however, was due to cumulative effect of hourly injections. The cumulative effect with hourly injections of regular insulin manifests itself between 4 and 6 hours, so the test should be run for at least 6 hours.

TABLE 6.—PATIENT F.T., 706-586, MEXICAN FEMALE, AGE 14.
(Patient fasting 14 hours before and during each test.)

SECTION 1.			SECTION 2.			SECTION 3.		
Blood sugars fasting.			Basal insulin determination Subcut. regular insulin.			Basal insulin determination I.V. Regular insulin.		
4-10-40.	Blood sugar, mg. per 100 cc.	Insulin.	4-19-40.	Blood sugar, mg. per 100 cc.	Insulin.	5-4-40.	Blood sugar, mg. per 100 cc.	Insulin I.V.
Time.			Time.			Time.		
Midnight	...	10	Midnight	...	20	Midnight	...	20* (subcut.)
7 A.M.	160	R.I.	7:12 A.M.	215.0		7:38 A.M.	160.0	
8	169		7:14	...	1½	8:16	...	2½
9	198		8:12	206.2		8:41	149.2	
10	200		8:14	...	2	9:15	...	1½
11	206		8:45	198.1		9:37	130.7	
12	204		9:12	...	1½	10:14	...	1½
			9:41	192.3		10:37	100.0	
			10:10	...	1½	11:16	...	1½
			10:37	185.0		11:41	144.9	
			11:10	...	1½	12:14 P.M.	141.8	
			11:35	142.0		1:15	...	1½
			12:40 P.M.	148.0		1:37	119.0	
			6 A.M. to 12 P.M.—5.3 gm. sugar in urine.			2:14	...	1½
						2:33	115.0	
						7:30 A.M. to 2:45 P.M.—no sugar in urine.		

* Subcutaneously.

(c). The requirement was calculated from the above as $2\frac{1}{2} +$ units per hour (16.5 units of insulin required in 6 hours, with the blood sugar 148.1 mg. per 100 cc. at the start and 111 mg. per 100 cc. at the end of the experiment).

The basal insulin determination in the same patient when regular insulin was given intravenously is seen in Sect. 3, Table 3. This was done to eliminate the factor of variability in the rate of absorption. In general, the method and results are similar. However, the initial intravenous dose was doubled because of mathematical considerations concerning the rate of destruction of intravenous insulin.^{2b}

The rate was between 2 and $2\frac{1}{2}$ units per hour by the intravenous route. (Sixteen units of insulin were given in 6 hours; the blood sugar was 156 mg. per 100 cc. at the start and 86.2 mg. per 100 cc. at the end of the test. The degree of fall in blood sugar was due to slightly too much hourly insulin, plus cumulative effect.)

The basal insulin determination by means of hourly injections of regular insulin (given either intravenously or subcutaneously), as

illustrated, is not practical for clinical use. For this reason we have devised a clinically applicable method.

We have found in a study of a group of 11 patients that there is a rough, general correlation between the total 24-hour insulin dose (disregarding diet) and the basal insulin requirement (Table 7). (The

TABLE 7.—TOTAL INSULIN DOSAGE AND BASAL REQUIREMENT PER HOUR.

Patient.	Total insulin dosage, 24 hours.	Carbo-hydrate.	Protein.	Fat.	Basal insulin requirement per hour, unit.
1. W.D. M 33	30	225	85	80	$\frac{1}{2}$
2. G.B. M 20	45-50	180	75	75	$\frac{3}{4}$ -1
3. J.D. M 56	40	200	85	90	$\frac{3}{4}$
4. E.T. M 14	85	250	85	80	1
5. U.T. F 18	65	100	60	80	1
6. J.Z. M 27	50	150	60	75	1
7. F.B. F 13	70	175	70	80	1 $\frac{1}{4}$
8. F.T. F 14	80	175	70	80	1 $\frac{1}{2}$
9. P.Q. M 23	70	180	75	100	2
10. B.P. F 15	95	150	65	80	2 $\frac{1}{2}$
11. M.F. F 44	130	150	75	100	3

dietary intakes varied from 1500 to 2150 calories.) This correlation may be summarized as follows:

1. When the 24-hour requirement of insulin is from 40 to 50 units the basal insulin requirement is between 0 and $\frac{3}{4}$ units per hour.

2. When it is 50 to 70 units the basal insulin requirement is between 1 to 1 $\frac{1}{4}$ units per hour.

3. When it is 70 to 100 units the basal insulin requirement is between 1 $\frac{1}{2}$ to 2 $\frac{1}{2}$ units per hour.

4. And when it is more than 100 units the basal insulin requirement is more than 3 units per hour.

After a severe diabetic is moderately well controlled by 3 or 4 injections of regular insulin daily an estimate of the probable basal insulin requirement can be made from the total dose, as tabulated above. To check the correctness of this estimated amount the following simple procedure can be performed by giving one injection of protamine zinc insulin and making 4 or 5 blood sugar determinations. The method is illustrated by Patient F. B. 698-247, Table 4, Sect. 3.

1. *Preparation for Test:* (a). The patient received no food within the 14 hours preceding and none during the test.

(b). Twenty units of regular insulin were given at midnight before the test to insure a blood sugar within the normal range at the start of the test.

2. *The Test:* (a). Ten units of protamine zinc insulin were given at 7:21 A.M. and blood sugar determinations were made at intervals of 2 hours during the next 8 hours. (The amount of protamine zinc insulin given was calculated as follows: The patient was receiving a

total of 70 units of regular insulin daily. From this figure the probable requirement was estimated as $1\frac{1}{4}$ units of regular insulin per hour, or 10 units of regular insulin for 8 hours. Empirically the same dose of protamine zinc insulin in one injection has been found to be effective in controlling the basal requirement during the night. This fact is supported by the statement of Lawrence,³ who says that 10 units of protamine zinc insulin last from 6 to 8 hours and 20 units 12 hours.)

(b). As seen by the chart there was a very negligible rise of the blood sugar—22 mg. per 100 cc.—from 9:35 A.M. to 3:25 P.M. This is in sharp contrast to the rise from 70 to 303 mg. per 100 cc. in 5 hours without insulin, seen in Sect. 1 of Table 4. The patient had received 20 units of insulin at midnight before each test. Thus 10 units of protamine zinc insulin covered the basal requirement for at least 8 hours in this patient.

The basal insulin requirement was determined with 1 dose of protamine zinc insulin in 3 patients in whom the more exact, tedious method with hourly injections of regular insulin had already been done. The requirement was found to be approximately the same, as seen in Table 3, Sect. 4; Table 4, Sect. 3; Table 5, Sect. 4.

Protamine zinc insulin is used to cover the basal requirement in preference to regular insulin, because of its slow, steady absorption and plateau type of activity. The basal insulin requirement exists 24 hours of the day, but is not a therapeutic problem except at night, since the insulin given to cover the diet is usually sufficient to cover the basal requirement during the day. The protamine zinc insulin to cover the night basal requirement is best given at the same time as the pre-dinner regular insulin. The amount needed is determined by multiplying the hourly requirement by the number of hours (12 to 15 hours) between dinner and breakfast as discussed above. Larger doses (40+ units) of protamine zinc insulin given before breakfast to cover the night basal requirement may cause hypoglycemia in the postabsorptive period at night.

The importance of the measurement of the basal insulin requirement lies in its therapeutic usefulness. We have demonstrated its value in regulating severe diabetics never previously well controlled.⁴ It is obviously advantageous for a severe diabetic to start the day with a normal blood sugar level.

Summary. 1. The basal insulin requirement of 5 severe diabetics was determined with regular insulin using both subcutaneous and intravenous injections. This requirement varied from $\frac{1}{2}$ to $2\frac{1}{2}$ units of insulin per hour.

2. A clinical method of measuring the basal insulin requirement with one injection of protamine zinc insulin is outlined.

3. The value of a basal insulin determination and its use in the control of the severe diabetic is discussed.

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INTERCAPILLARY GLOMERULOSCLEROSIS (KIMMELSTIEL- WILSON) AND THE NEPHROTIC SYNDROME IN DIABETES MELLITUS.

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IN 1936 Kimmelstiel and Wilson⁴ described a distinctive lesion of the renal glomeruli and called attention to its association with a clinical complex of diabetes mellitus, hypertension and a nephrotic syndrome. To this lesion they gave the name "intercapillary glomerulosclerosis" because they believed it to be a sclerotic thickening of the intercapillary connective tissue. Apart from its occurrence in the intracapillary type of glomerulonephritis, the lesion was found in only 8 cases, of which 7 were diabetic, out of the entire post-mortem material which they studied. They concluded that "only a small proportion of diabetics appear to show this lesion."

In 1938 Anson² studied the kidneys in 900 cases, and found the changes characteristic of "intercapillary glomerulosclerosis" only 6 times. He confirmed its correlation with diabetes and hypertension but in only 2 instances with the nephrotic syndrome. Since then 2 more small series of cases have been published in which the clinical data have been more completely presented.^{3,6} They support the thesis that the lesion described by Kimmelstiel and Wilson is almost always associated with diabetes, with hypertension, with profuse albuminuria and often with a nephrotic syndrome. Nonetheless, further study is warranted to ascertain whether the lesion occurs among non-diabetics, apart from glomerulonephritis, and whether in the diabetic cases it is invariably associated with the clinical findings mentioned above. In undertaking this study, we were stimulated by our previous interest in the association of a nephrotic

* Work done during tenure of George Blumenthal, Jr., Fellowship in Pathology.

picture with diabetes⁸ and by the hope that some further light might be shed upon the problem of the pathogenesis of the nephrotic syndrome.

The *postmortem material* studied comprises cases falling into the following clinical categories: (Table 1).

TABLE 1.—CLINICO-PATHOLOGIC CORRELATION.

Clinical classification.	No. of cases.	Kimmelstiel-Wilson lesions.					
		Present.	Grade of development.				Absent.
			1.	2.	3.	4.	
Control series: non-diabetic, non-hypertensive	100	0	100
Control series: non-diabetic with hypertension	100	1	1	..	99
Diabetic series	105	35	16	9	8	2	70
Group 1: no hypertension; no renal complication	60	12	10	2	48
Group 2: hypertension; no renal complication	27	9	4	4	1	..	18
Group 3: partial or complete renal syndrome	18	14	2	3	7	2	4*

* Includes 1 case of renal amyloidosis.

A. One hundred consecutive non-diabetic control cases, without hypertension. All ages were included.

B. One hundred consecutive non-diabetic cases with hypertension, all 40 years of age or more. A blood pressure of 160/90 or more was considered abnormal.

C. One hundred and five consecutive cases of diabetes 40 years of age or older. These cases were classified clinically into three groups. The first and second groups included those with slight or no evidence of renal damage. The second group differed from the first in the presence of hypertension. The third group comprised cases with hypertension and with definite signs of renal damage, often with partial to complete development of a nephrotic syndrome.

The diabetic kidneys were graded as to the degree of development and extent of the Kimmelstiel-Wilson lesion. The 1+ kidneys averaged 1 to 5 lesions per microscopic section, whereas the 4+ kidneys contained lesions in almost every glomerulus. The diabetic cases which had been classified solely on clinical grounds were then correlated with these pathologic findings.

Special stains for collagenous and elastic tissue (Mallory's aniline blue, phosphotungstic acid hematoxylin, azocarmine, and Weigert's combined with Van Gieson) and for amyloid and fat deposits were applied when indicated.

The *clinical material* consists of 11 additional cases which have

been reported elsewhere.⁸ These illustrate the occurrence of a nephrotic syndrome in diabetes. Each of the 11 cases would be classified clinically in Group 3 (Table 1) as noted above. Four of these cases have been autopsied and the kidneys studied and graded as to the development of the glomerular lesion in the manner already described.

Results. *Clinico-pathologic Correlation.* Table 1 shows that the Kimmelstiel-Wilson lesion was absent from the kidneys of all the non-diabetic control cases without hypertension. This group included a wide range of medical and surgical conditions. In the second control series of non-diabetic cases with hypertension, only 1 out of 100 revealed the specific glomerular change. The special interest which attaches to the unusual occurrence of this lesion in the absence of diabetes warrants the presentation of this case in some detail:

Intercapillary Glomerulosclerosis in a Case of Hypertension Without Diabetes.

Case 451955; PM 11419. A 51-year-old Italian housewife with a 15-month history of hypertension, edema and dyspnea. No personal or family history of diabetes. Examination revealed obesity, slight dyspnea. Fundi: arteriovenous compression, hard exudates and hemorrhages. Signs of fluid in both pleural cavities. Edema of abdominal wall, upper and lower extremities. B.P. 160/90. Laboratory findings: Hemoglobin, 86%; urine: 3+ albumin, moderate casts; Esbach: 4 gm. per liter. No glucose in 3 specimens. Venous pressure 15 cm. Blood urea N 60 mg. per 100 cc.; total protein 6 gm. per 100 cc.; glucose 85 mg.; cholesterol 240 mg. Patient's course was one of progressive cardiac failure. Autopsy: hypertrophy and dilatation of ventricles; diffuse myofibrosis cordis; moderate sclerotic narrowing of LAD coronary artery branch; congestion of viscera; mild benign nephrosclerosis. The kidneys weighed 360 gm. together, the capsules stripping with slight difficulty, leaving a very finely granular purplish-gray surface. Cut surface showed sharp cortico-medullary differentiation. Renal sections: much cortical atrophy. The Kimmelstiel-Wilson lesions were typical and were of Grade 3. Marked arteriolosclerosis. Moderate amount of fat in arterioles and convoluted tubules (Fig. 1.)

Apart from the consecutive series of control cases a second instance of the occurrence of the advanced Kimmelstiel-Wilson lesion in nephrosclerosis without diabetes was accidentally encountered. As in the case just presented, there were evident signs of renal damage such as profuse albuminuria, tendency to hypoproteinemia, marked edema and nitrogen retention. Although arteriolosclerosis of the kidneys and cardiac failure might in each instance have been sufficient to cause these phenomena, it is probable that as in the diabetic cases the "intercapillary glomerulosclerosis" has contributed to the renal picture.

In the series of 105 diabetics the Kimmelstiel-Wilson lesion was found in 35 cases. Table 1 shows the close correlation in the degree and extent of the lesion with the degree of development of the renal syndrome. Thus the lesion was present in 14 of 18 cases showing definite clinical signs of a renal complication (Group 3). In 9 of

these the lesion was in an advanced stage. In contrast, only 12 of the 60 diabetics without hypertension or renal damage (Group 1) showed the lesion and then generally in an incomplete stage of development. In such cases the lesion might even be limited to a single glomerulus in a microscopic section. However, they are identical with those described by Kimmelstiel and Wilson and they cannot be distinguished from those seen in sections containing other lesions in a more advanced and obvious stage. The occurrence of this form of glomerulosclerosis in the absence of profuse albuminuria, edema, hypertension, eye ground changes, or other criteria of the renal

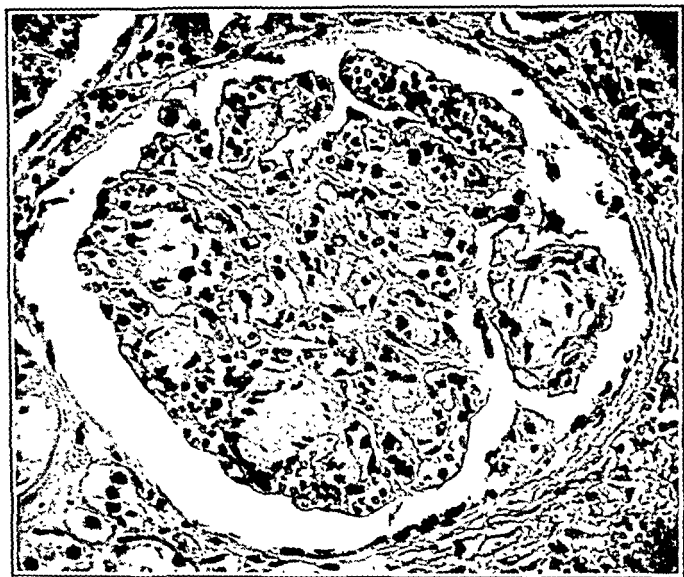


FIG. 1.—PM, 11419. Intercapillary glomerulosclerosis in a case of hypertension without diabetes.

complication with which it has come to be associated, is of some theoretical importance. One of these cases may deserve detailed presentation to illustrate this point more clearly.

Intercapillary Glomerulosclerosis in Diabetes Without Hypertension or Renal Syndrome.

Case 421959; PM 10797. A 67-year-old Jewish housewife with a past history of several gall bladder attacks, admitted with the complaint of anorexia, asthenia and jaundice of 4 weeks' duration. Diabetes of 10 years' duration controlled by diet alone. Physical examination: B.P. from 120/60 to 150/60. Fundi negative. Precordial systolic murmur. Liver huge, slightly tender. No edema. Moderate icterus. Laboratory findings: Hemoglobin 60%. Urine: albumin faint trace, trace and 1+ on three occasions; occasional casts. Blood urea nitrogen 23 mg. per 100 cc.; glucose 220 mg.; cholesterol 1000 mg.; total protein 7.1 mg. Icterus index 20. Patient died several weeks after operation because of subdiaphragmatic abscess. Procedure was cholecystectomy and choledochotomy for stone. Autopsy: moderate coronary atherosclerosis; mild benign nephrosclerosis; left subdiaphragmatic abscess. The kidneys weighed 325 gm. together and

showed fine granularity of the surface. Histologic sections: slight degree of arteriosclerosis and arteriolosclerosis. The Kimmelstiel-Wilson lesions were of Grade 2 (Fig. 2).

Cases such as these suggest strongly that the Kimmelstiel-Wilson lesion does not depend upon the presence of appreciable nephrosclerosis for its development and that it may occur without clinical evidence of significant renal damage. Its relationship with diabetes is all the more emphasized inasmuch as this is the one element of the triad of diabetes, hypertension and albuminuria⁶ which is almost constantly present. However, as we have already seen, this too may in rare instances be absent.

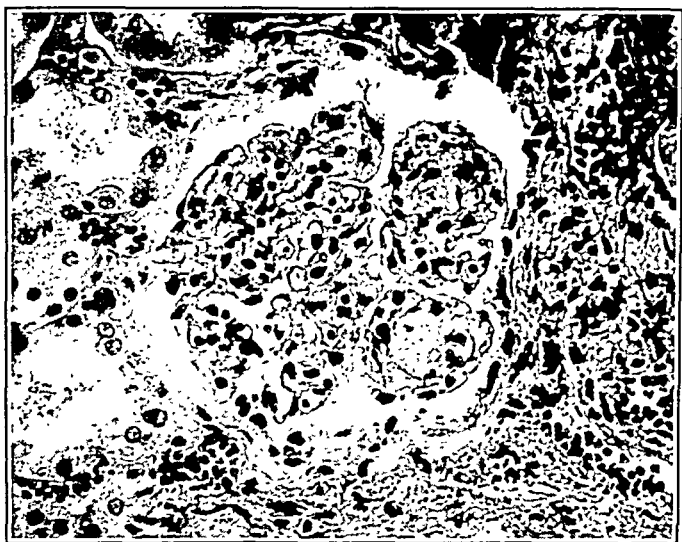


FIG. 2.—PM, 10797. Intercapillary glomerulosclerosis in a case of diabetes *without* hypertension or the elements of the nephrotic syndrome.

The Clinical Syndrome With Advanced Glomerulosclerosis. The salient clinical features of 10 cases from the consecutive series of diabetics in which the Kimmelstiel-Wilson lesions were found in an advanced stage, Grades 3 or 4, are shown in Table 2. No constant clinical syndrome characterizes these cases, although a tendency to marked albuminuria and hypoproteinemia may be present. The clinical findings in this type of case often may be distinctive enough to warrant a diagnosis of "intercapillary glomerulosclerosis." Coronary thrombosis, heart failure or peripheral vascular disease may dominate clinical attention. However, in 3 instances (Cases 8, 9, and 10; Table 2) the renal complication was prominent enough to be readily recognized clinically. Case 10 illustrates the fullest development of the renal syndrome with marked edema, lowered total blood proteins, increased blood cholesterol, hypertension, and termination in uremia. Such a clinical syndrome occurring in a middle-aged mild diabetic warrants the diagnosis of this type of renal lesion.

TABLE 2.—ADVANCED GLOMERULOSCLEROSIS (KINNELSTIEL-WILSON) IN DIABETES. CLINICAL FEATURES OF TEN CONSECUTIVE AUTOPSED CASES.

CLINICAL FEATURES OF TEN CONSECUTIVE AUTOPSIED CASES.																		
Case No.	Age.	Sex.	Diagnosis and clinical course.	Diabetes.		Blood pressure.	Edema	Eye ground changes.	Cardiac failure.	Urine.				Blood.				
				Duration, yrs.	Insulin need, units.					Albumin.	Sp. gr., max.	R.B.C.	Cast.	Glu- cose.	Total protein, alb. glob.	Choles- terol.	Urea nitro- gen.	Hgb., %.
413717 (1)	60	F	Essential hypertension Fractured neck of femur	16	15	240/140	0	=	=	2+ 4 G/L	1.014	0	=	210	N.R.	600	39	52
374641 (2)	60	M	Diabetic gangrene Arteriosclerotic heart disease	14	0	168/92	N.R.	3+	3+	3+	1.018	0	2+	190	N.R.	N.R.	45	55
413383 (3)	55	F	Coronary thrombosis Multiple carbuncles	15	0	160/90	1+	Myopia	1+	1+	1.018	0	=	550	5.6 (2.8, 2.8)	310	34	71
371058 (4)	65	F	Diabetic gangrene Bronchopneumonia	3	10	195/80	0	N.R.	0	4+	1.015	0	=	255	5.6 (3.1, 2.5)	270	24	N.R.
447456 (5)	70	M	Arteriosclerotic heart disease Coronary thrombosis Congestive failure	2	0	160/90	2+	2+	2+	4+ 5 G/L	1.024	0	4+	230	6.0	315	38	60
453119 (6)	52	F	Gas gangrene Diabetic retinitis Uremia	6	0-10	130/72	2+	4+	3+	4+	1.034	0	=	230	5.6	N.R.	50	74
395731 (7)	52	F	Pyelonephritic contracted kidney Cardiac failure Coronary thrombosis	5	20	220/95	0	N.R.	3+ (left)	Trace	1.012	=	0	205	N.R.	450	39	45
398307 (8)	51	F	Arteriosclerotic heart disease Old coronary thrombosis	10	40	150/100	4+	3+	4+	3+	N.R.	0	0	280	5.2 (2.5, 2.7)	535	16	90
385838 (9)	61	F	Hypertensive heart disease Lobar pneumonia	11	20-40	240/116	3+	=	1+	3+	1.028	0	=	215	5.3 (2.8, 2.5)	830	30	62
449648 (10)	55	F	Arteriosclerotic heart disease Uremia Peripheral neuropathy	5	25	190/100	3+	1+	2+	4+ 8 G/L	1.014	0	3+	220	4.7 (2.7, 2.0)	440	131	75

G/L in albumin column = grams per liter (Esbach).

G/L in albumin column = grams per liter (Esbach).

As previously reported,⁸ a syndrome closely simulating the clinical picture and course of chronic glomerulonephritis is not an uncommon occurrence among middle-aged or elderly diabetics. Such cases are especially characterized by the development of a nephrotic syndrome. Table 3 presents 11 such cases, of which only 4 (Cases 1 to 4) have been autopsied, all showing the Kimmelstiel-Wilson lesions in an advanced stage, Grades 3 or 4.

The following case illustrates the characteristic clinical course of these cases which develop the complete renal syndrome:

Intercapillary Glomerulosclerosis in a Diabetic With Hypertension and Nephrotic Syndrome.

History. Adm. 437064. The patient, a 55-year-old negress, had been under observation in the diabetes clinic since 1935. Her family history was of no significance. Her past history was negative. There was no history of scarlet fever, kidney disease, or of hypertension. She complained of marked loss of weight, moderate polydipsia, and polyuria of several months' duration. Five per cent glucose and a trace of albumin were discovered in the urine. Her blood pressure was 158/90. Her diabetes was mild and readily brought under control on a diet of 120-60-60 with 10 units of regular insulin daily.

A tendency to unusually rapid weight gains was noted within the first few months of observation; but it was not until 1937, after a rather long lapse in clinic attendance, that the appearance of edema was first observed. At this time, she also had shooting pains in the left leg and a sensation of deadness in both hands. She had had swelling of the legs for several months but no dyspnea or precordial pain. There was a hypertension of 190/90, a tachycardia of 116, and moderate pretibial pitting edema.

In the light of previous experience with similar cases, the cause of the edema was forthwith sought in hypoproteinemia. The blood total protein was found to be 4.4 gm. per 100 cc. with albumin and globulin fractions each 2.2 gm. per 100 cc. Blood cholesterol was 535 mg. per 100 cc. The urine contained a heavy trace of albumin with some casts and a rare red blood cell.

It was apparent then that the patient presented the clinical and laboratory findings of the nephrotic syndrome as seen in the course of chronic glomerulonephritis. She was referred to the hospital wards for more intensive study and therapy.

Examination. The pupils were equal, reacting to light and in accommodation. The lungs were negative; there was no evidence of pleural effusion. The heart was not enlarged. There was a regular sinus rhythm with no murmurs. The liver was palpable two finger-breadths below the costal margin. Slight dullness was present in both flanks, with a fluid wave. There was moderate dependent edema. The peripheral pulses were patent. The deep reflexes were equal and active. The blood pressure was 170/100. The fundi were described by the ophthalmologist as showing slight narrowing of the arteries. The neurologic consultant found only slight evidence of peripheral neuropathy, namely, diminution of vibration sense in both lower extremities, pain and touch being only slightly affected.

Laboratory Data. Hemoglobin 63%; R.B.C. 3,900,000; W.B.C. 7100 with a normal differential count; blood urea nitrogen 15 mg. per 100 cc., glucose 160 mg. per 100 cc., cholesterol 470 mg. per 100 cc. and total proteins 5.4 gm. per 100 cc. (albumin 2.6, globulin 2.8). The blood Wassermann reaction was negative. The urine showed from a very faint trace to 2+ albumin, the Esbach test showing as much as 2 gm. per liter. There

TABLE 3.—THE NEPHROTIC SYNDROME IN DIABETES.

Case No.	Age.	Sex.	Diagnosis and clinical course.	Diabetes.		Blood pressure.	Edema.	Eye ground changes.	Cardiac failure.	Urine.				Blood.				
				Duration, yrs.	Insulin need, units.					Albumin.	Sp. gr., max.	R.B.C.	Casts.	Glucose.	Total protein, alb. glob.	Cholesterol.	Urea nitrogen.	Hgb., %.
401506* (1)	50	M	Chronic glomerulonephritis Died in uremia and heart failure	½	0	190/130	3+	3+	3+	3+ 3 G/L	1.024	1+	1+	181	4.5 (2.2, 2.3)	375	139	88
409473* (2)	44	M	Malignant hypertension(?) Chronic glomerulonephritis Death in uremia and heart failure after 2 years	1¼	0-15	220/140	2+	4+	2+	3+	1.018	0	3+	236	5.1 (2.9, 2.2)	650	61	62
414048* (3)	56	F	Chronic glomerulonephritis Death in uremia 2 years after onset	12	0-15	200/110	4+	4+ blindness	3+	4+ 8.5 G/L	1.020	2+	1+	175	4.4 (2.2, 2.2)	750	75	53
437064*† (4)	55	F	Chronic glomerulonephritis Death after 2 years in uremia and heart failure	4	0-20	230/120	4+	2+	3+	3+ 2.5 G/L	1.017	1+	1+	200	4.4 (2.2, 2.2)	535	114	52
383304 (5)	54	F	Chronic glomerulonephritis Death in uremia 3 years after onset	7	25-30	210/90	4+	4+	=	4+ 6.6 G/L	1.016	0	1+	265	4.8 (2.4, 2.4)	775	73	43
372041 (6)	50	F	Chronic glomerulonephritis Hypertensive heart disease Death in heart failure after 3 years	20	15-30	180/90	4+	2+	4+	3+	1.012	=	1+	310	5.6 (3.2, 2.4)	675	50	60
434532 (7)	49	M	Chronic glomerulonephritis	10	0-20	200/110	2+	2+	1+	3+ 3 G/L	1.022	=	1+	155	4.2 (1.8, 2.4)	500	51	80
420499 (8)	73	M	Chronic glomerulonephritis Essential hypertension	5	0	200/100	2+	3+	0	2+	1.018	2+	2+	230	5.2 (3.1, 2.1)	410	40	70
440450 (9)	48	F	Chronic glomerulonephritis Death in uremia 2 years after onset	½	0	200/90	3+	2+	0	3+	1.023	=	3+	180	4.9 (2.8, 2.1)	625	153	70
457272 (10)	46	F	Hypertensive heart disease Congestive heart failure Alive 4 years after onset	9	0-30	210/110	3+	2+	3+	3+ 4 G/L	1.020	0	3+	200	4.6 (1.9, 2.7)	500	84	80
38-520 (11) (O.P.D.)	66	M	Diabetic glomerulosclerosis	6	0	212/112	3+	=	0	4+	1.016	=	1+	280	4.8 (3.4, 1.4)	370	12	72

* Cases autopsied all showing lesions of intercapillary glomerulosclerosis, Grades 3 or 4.

† Case presented in text.

G/L in albumin column = grams per liter (Esbach).

was an occasional hyaline cast and a rare red blood cell. The urine concentrated to a specific gravity only of 1.017.

The venous pressure was 5 cm.; circulation time measured by the saccharine method was 12 seconds. These determinations gave the clinical impression that circulatory failure played no rôle whatsoever in the production of the edema. The electrocardiogram showed left axis deviation QRS complex slightly slurred with moderately low voltage, and T_i isoelectric.

Course. Under observation for a period of 19 days, the patient's diabetes was brought under control on a regimen of 150 gm. CHO, 150 gm. protein, and 120 gm. fat without insulin. The edema disappeared on this diet and bed rest, without the use of diuretics. The albuminuria decreased. The total protein rose to 6.2 gm. per 100 cc., but of this the albumin fraction remained 2.5 gm.

Because of the ready response to treatment, the patient was discharged with the diagnosis of diabetes mellitus and essential hypertension. The edema and hypoproteinemia were thought to be due to malnutrition caused by strict adherence to a limited diabetic diet.

She remained under close observation in the diabetic clinic and two subsequent hospital admissions during the next 2 years. The clinical course was such as to modify the former somewhat optimistic impression as evidence of cardiac and renal failure appeared. Despite faithful adherence to a high protein regimen, there was a reaccumulation of edema, the low blood proteins persisting (5 gm. per 100 cc., albumin 2.2, globulin 2.8), together with an increased blood cholesterol level (765 mg. per 100 cc.) and profuse albuminuria.

Two further laboratory findings are to be noted. A Congo red test showed only 35% retention, indicating the absence of amyloidosis. A glucose tolerance test confirmed the presence of moderate diabetes.

The blood pressure tended to rise, reaching 230/120; marked hypertensive retinopathy with hemorrhages and exudates appeared; there was increasing evidence of cardiac enlargement and insufficiency. In the last few months of observation, azotemia set in with a blood urea nitrogen rather rapidly rising to 114 mg. per 100 cc. The patient was discharged from the hospital in a state of suburemia and several weeks later she died in coma.

Necropsy Findings. General anasarca was present. The heart was enlarged, weighing 500 gm. The lungs were congested and edematous. The liver was congested. The pancreas showed postmortem autolysis. The kidneys were distinctly enlarged, weighing 200 gm. each. The capsules stripped easily leaving a yellowish-gray surface, smooth except for small foci showing the finest granularity. The cut surface revealed a yellowish-gray cortex, fully 6 mm. thick, which was fairly well demarcated from the medulla. The glomeruli were purple-red. Histologic sections showed widespread distribution of Kimmelstiel-Wilson lesions involving almost every glomerulus. There was extreme arteriolosclerosis and moderate to marked arteriosclerosis. There was much fat in the walls of the thickened, hyalinized arterioles and a moderate amount in the epithelium of the convoluted tubules, the capillary loops of the glomeruli, and in Bowman's space. The Kimmelstiel-Wilson lesions were graded 4+.

Differential Clinical Features. The following clinical features of cases of this type (Table 3) deserve special emphasis: 1, Age group: all 11 patients were 44 years of age or over. 2, Type of diabetes: the diabetes was mild, requiring little or no insulin for adequate control. 3, Chronologic relationship of the diabetes and the renal syndrome: This is difficult to state categorically for both conditions are characterized by insidiousness of onset. The diabetes apparently

preceded the renal disease by from 5 to 20 years in 5 cases, and by 1 to 5 years in 2 cases. Of the remaining 4 patients, the diabetes was discovered several months before the renal disease in 2, whereas in 2 others, the symptoms and signs of the renal state developed a few months before the discovery of the diabetes. 4, Peripheral neuropathy: 1 of these patients (Case 6) presented such neurologic findings of severe enough degree to warrant the diagnosis of pseudotabes. In 2 others, the evidence of peripheral nerve involvement was slight (see also Case 10, Table 2). The tendency to peripheral neuropathy in these cases appears to support the hypothesis of a vascular etiology of this neural complication of diabetes.⁹ 5, Hypertension: a systolic blood pressure of 190 or more, with a diastolic level about 100, was observed in all 11 patients. In 1 instance only (Case 2) was the hypertension so marked and the

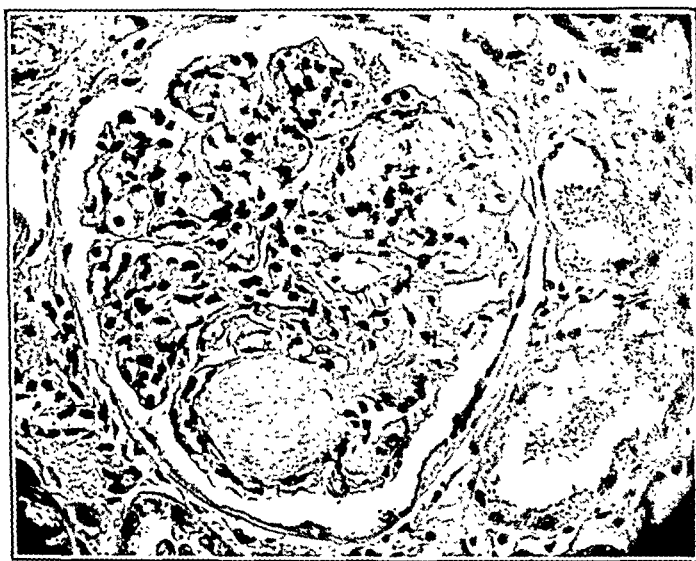


FIG. 3.—PM, 11448. Intercapillary glomerulosclerosis in a case of diabetes with hypertension and the nephrotic syndrome (Case 10, Table 2).

clinical course so accelerated as to suggest the possibility of malignant hypertension. 6, Eye ground changes: 10 of the 11 cases showed moderate to marked hypertensive retinopathy, often with evidence of concomitant diabetic changes. Edema of the disk was common in addition to severe arterial damage, hemorrhages, and exudates. These findings, in general, paralleled the course of the disease into renal failure. Retinal damage was more marked than is ordinarily seen in benign essential hypertension but quite comparable to the usual findings in advanced chronic glomerulonephritis. 7, Cardiac failure: some degree of myocardial decompensation was present in 8 of the 11 patients either coexistent with the nephrotic picture or appearing later. 8, Azotemia: nitrogen reten-

tion was present in 10 cases, progressing to uremia in 6. 9, Prognosis: 7 of the 11 cases died within 2 to 3 years of the onset of the renal syndrome, death being due to uremia, cardiac failure or both.

These cases are not clinically identical with the nephrotic phase of chronic glomerulonephritis. Hypertension, heart failure, and severe eye ground changes are more frequently present than in the analogous stage of nephritis. An important clinical difference is that the diabetic cases fall into an older age group, usually 45 years of age or more. In contrast, the records of the Mt. Sinai Hospital from 1933 to 1938 reveal that of 93 non-diabetic patients with the nephrotic syndrome, only 10 were 45 years or older.

Discussion. The results of the investigation here presented broadly confirm the conclusion of Kimmelstiel and Wilson as to the existence of a relationship between the form of glomerulosclerosis which they described and a clinical syndrome of which the characteristic features are "diabetes, severe and widespread edema of the nephrotic type, and gross albuminuria. Hypertension is frequently present, in many cases associated with renal decompensation."⁴ However, the relatively frequent occurrence of the lesion in the diabetic kidney does not appear to have been appreciated. Its presence in cases of diabetes without a renal complication strongly suggests that this type of glomerular change precedes and, when fully developed, is probably the cause of the renal syndrome. It excludes the possibility that these lesions are merely secondary to marked nephrosclerosis or somehow the result of profuse albuminuria. The parallelism of development between the Kimmelstiel-Wilson lesions and the clinical picture of the renal complication supports this concept of a causative relationship.

The occurrence of the Kimmelstiel-Wilson lesion in 2 cases of hypertension without diabetes is of great interest. The theory that diabetes is the sole etiologic factor in the development of this form of glomerulosclerosis is thus rendered untenable. This is further borne out by the fact that the lesion does not seem to occur in the course of severe diabetes and that the diabetes does not always antedate the renal syndrome. A possibility which may deserve discussion is that perhaps the same specific form of vascular damage affects both the renal glomeruli and the pancreatic islets. However, one of the authors has been unable to discover any unusual islet lesion in such cases nor is there a higher incidence of islet hyalinization in diabetes with intercapillary glomerulosclerosis than in cases without it.¹ Apparently, one must look elsewhere for the fundamental etiologic mechanism which produces both diabetes and this form of renal damage.

It is incidentally suggested¹ that the presence of intercapillary glomerulosclerosis in one-third of the diabetic cases makes this lesion of value in the postmortem diagnosis of diabetes mellitus. It is pointed out that the histologic criteria hitherto employed, such as

hyalinization of the pancreatic islets, and glycogen distribution are notoriously unreliable and difficult of interpretation. The advantages of the use of this lesion for this purpose are its ease of recognition with ordinary stains, the fact that it requires no special fixative, and, finally, that it is especially common in mild cases of diabetes where such a diagnostic clue is of particular value.¹

The proneness of the middle-aged, mild, hypertensive diabetic to this type of renal complication, the clinical course of which may closely simulate chronic glomerulonephritis, is a fact of some clinical importance. Especially striking is the development of a partial to complete nephrotic syndrome. Young patients with severer grades of diabetes do not appear to develop this form of renal damage. A nephrotic syndrome in such patients is much more likely to be due to diffuse glomerulonephritis than to intercapillary glomerulosclerosis.⁵

Edema in the course of diabetes has in the past generally been regarded as a transient manifestation often nutritional in origin or due to therapy.⁷ However, edema or persistent profuse albuminuria in the middle-aged diabetic should not be viewed lightly but should be taken as a possible warning of an impending renal complication of serious import. It is now clear that the vascular vulnerability of the diabetic may affect the kidneys as significantly as it does the heart or peripheral vessels.

Summary and Conclusions. 1. No instance of glomerulosclerosis of the Kimmelstiel-Wilson type was found in 100 consecutive cases without diabetes or hypertension.

2. In a series of 100 consecutive non-diabetic hypertensives this lesion occurred but once. The clinical and pathologic features of this case are presented in detail.

3. Intercapillary glomerulosclerosis was found in 35, or one-third, of 105 diabetics. This lesion was present in 12 of 60 diabetics *without* hypertension or a renal complication, and in 14 of 18 diabetics with clinical evidence of renal damage.

4. There appears to be a definite relationship between the degree of involvement of the kidneys by this form of glomerulosclerosis and the development of the clinical picture. However, of 10 cases with this lesion in an advanced stage, only 3 presented a complete renal syndrome.

5. The occurrence among middle-aged, mild hypertensive diabetics of a clinical syndrome closely simulating chronic glomerulonephritis, with a nephrotic phase and often with termination in renal failure, is emphasized.

6. Attention is drawn to the value of this lesion as a useful histologic criterion in the postmortem diagnosis of diabetes mellitus.

The authors wish to express their gratitude to the Montefiore Hospital and Office of the Chief Medical Examiner of New York City for permission to study autopsy material and clinical records.

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A CONSIDERATION OF CERTAIN BIOLOGICAL DIFFERENCES BETWEEN GLOMERULONEPHRITIS AND RHEUMATIC FEVER.

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CLINICAL,^{18b,19a,32,42,48} bacteriologic,²⁰ and immunologic^{19,22,37,39} data indicate that the initiation of glomerulonephritis is in most instances related to Group A hemolytic streptococcus infection. Comparable studies on the etiology of rheumatic fever^{5b,5a,b} point to the same initiating agent. Despite the fact that the initiating agent may be the same for both diseases, it has become apparent that certain fundamental biologic differences exist between the natural history of glomerulonephritis and that of rheumatic fever. A consideration of certain of these differences is herewith presented.

Differences in the Geographic Distribution of Acute Glomerulonephritis and Rheumatic Fever. There appears to be common agreement^{11,14,27,38,43,49} that rheumatic fever is more common in the northern than in the southern latitude regions of North America. In contrast, it has been shown⁴¹ that no such geographic variation in the incidence of acute glomerulonephritis is present in the data compiled from the records of selected hospitals in the northern and southern latitude areas of North America.

When these facts are considered in the light of the geographic distribution of Group A hemolytic streptococcus infections, certain puzzling problems are raised. Coburn^{6b} has reported that the hemolytic streptococcus occurs in the throat flora only rarely and in small numbers in selected individuals studied in subtropical San Juan, Puerto Rico. Morales-Otero and Pomales-Lebrón^{24a} have found

that the incidence of beta hemolytic streptococci in normal throats of inhabitants of San Juan, Puerto Rico, is 4 to 9%. Only 22.6% of the strains isolated belonged to Group A. Seasonal variations in the carrier rate were negligible. Additional data obtained by these workers are contained in the summary: "In single throat cultures from persons suffering from tropical lymphangitis, the incidence was 20 per cent, and in serial cultures, the incidence came up to 29 per cent. From persons with a history of recent sore throat, hemolytic streptococci were cultured in 30 per cent. From 100 pairs of excised tonsils, hemolytic streptococci were isolated in 33 per cent. . . . Hemolytic streptococci are not found here (San Juan) in *normal* throats as frequently as they are in New York City. On the other hand, we frequently isolate beta hemolytic streptococci from diseased tonsils, skin sores, pustules, abscesses, cases of lymphangitis, etc., and these strains are indistinguishable from those isolated in New York City." Teiger and B. C. Seegal⁴⁵ have also shown that strains of beta hemolytic streptococci isolated from the pharynx of normal individuals and patients ill of tonsillitis or acute nephritis in New Orleans are indistinguishable by the usual tests from the beta hemolytic streptococci isolated from similar individuals and patients in New York City.

Recent studies by Morales-Otero and Pomales-Lebrón^{24c} in San Juan, Puerto Rico, show that significantly elevated antistreptolysin titers are found in the sera of many individuals with a history of previous pharyngitis. A previous report by these workers^{24b} had indicated that hemolytic streptococcus infection played a significant rôle in recurrent tropical lymphangitis since the antistreptolysin titers in subjects ill of this disease were increased above normal levels.

Plummer³³ has presented additional evidence on immunologic grounds pointing to the presence of a considerable degree of hemolytic streptococcus infection in tropical areas. Sera obtained from students and laboratory workers in Toronto, Canada, were compared with the sera obtained from individuals in the tropical areas of Madras, Punjab, Manila, East Africa and South America in order to test their potency with respect to hemolytic streptococcus antitoxin. In subjects of all ages, 1 cc. of serum contained more than one Washington unit of streptococcal antitoxin in 64.6% of 254 Canadian, and in 93.5% of tropical sera. The mean potency of the tropical sera was significantly greater than those of the temperate zone. For subjects under 17 years of age, 44% of 50 Canadian, and 93% of 45 tropical sera contained more than one unit of antitoxin per cc. The mean potencies differed significantly. For adults, 69.6% of 204 Canadian and 93.5% of 62 tropical sera contained more than one unit of antitoxin per cc. The mean potencies were not significantly different.

These immunologic facts suggest that invasion by the Group A

hemolytic streptococcus capable of producing antitoxin as well as antistreptolysin is as prevalent in subtropical and tropical zones as in the temperate zone. It is not possible with our present state of knowledge to explain the variation in the geographic distribution of rheumatic fever and acute glomerulonephritis. However, it may be possible that the character and site of the primary focus varies for these zones. This possibility is considered later.

In summary, it is apparent that two diseases of presumable hemolytic streptococcus origin, acute glomerulonephritis and rheumatic fever, present a biologic difference with respect to geographic distribution. The incidence of rheumatic fever is conditioned by climate. The frequency of the disease is diminished in the southern as compared with the northern latitude regions of North America. This difference is not apparent in similar studies of the latitude frequency of acute glomerulonephritis. In this respect it is of considerable interest that immunologic tests for hemolytic streptococcus antitoxin and antistreptolysin indicate the presence of the hemolytic streptococcus in subtropical and tropical regions in which rheumatic fever is of low incidence and acute glomerulonephritis is of "normal incidence." The possible significance of the character of the infectious tissue focus in this difference is to be discussed elsewhere.

TABLE 1.—SEX INCIDENCE IN GLOMERULONEPHRITIS.

Reference.	Type of glomerulonephritis.	Total cases.	Male : female.	Notes.
Osman ³⁰	Acute	Males outnumber females in all age groups except 16-20
Seegal, Seegal and Lyttle ⁴²	Acute	379	2 to 1	All ages
Lyttle <i>et al.</i> ²² . . .	Acute	116	2 to 1	95 patients under 13 yrs. of age
Schwarz, Kohn and Weiner ³⁵	Acute	244	2 to 1	All ages
Futcher ¹²	Acute, after skin or wound infections	11	2 to 1	
Loeb <i>et al.</i> ¹⁷	Chronic	73	2 to 1	All ages; 43% under 20 yrs. of age
Ollayos and Peters ²⁸	Acute	275	2 to 1	All ages

Comparison of the Sex Incidence in Glomerulonephritis and Rheumatic Fever. All reports are in agreement that acute glomerulonephritis is more common in the male. The findings of a number of workers are collected in Table 1. From these figures it may be seen that males outnumber females about 2 to 1 in all types of glomerulonephritis in the reported series.

No such unanimity as to the sex incidence in rheumatic fever is apparent from published data. It is difficult to obtain satisfactory statistics on this point probably, for two reasons: 1, the various rheumatic manifestations apparently have different sex incidence; 2, many institutions caring for rheumatic children select their cases,

having a set number of beds for each sex. A number of reports on this subject are presented in Table 2. Although there is considerable variation in the figures, there seems to be a fairly equal distribution of the two sexes for the entire group. The report of

TABLE 2.—SEX INCIDENCE IN RHEUMATIC FEVER.

Reference.	Type.	Total cases.	Male, %.	Female, %.	Notes.
Brooks and O'Regan ³	Acute rh. fever	700	63	37	7% children
DeGraff and Lingg ⁹	" " "	1633	56	44	Females predominate to 13 years of age
Dally ⁸	" " "	300	39	61	Children only
Hench <i>et al.</i> ¹⁵	" " "	..	40	60	
Dieuaide ¹⁰	" " "	141	62	38	Ratio 1 to 1.36, however, when figures are corrected for hospital admissions
Swift ^{4a}	" " "	..	50	50	
Wilson, Lingg and Croxford ⁴⁷	Rh. heart disease	395	39	61	Children
Coombs ⁷	" " "	687	34	66	All ages
St. Mary's Home ⁷ (Pub. cit.)	" " "	321	43	57	
Osler and MacCrae ²⁹	" " "	..	70	30	
Collective Investigational Reports ²⁹ (Pub. cit.)	" " "	654	57	43	
Cabot ¹	" " "	120	53	47	Necropsied cases
	" " "	239	46	54	O.P.D. cases
	" " "	315	42	58	Total living cases
	" " "	150	35	65	Mitral stenosis
Torrey ⁴⁶	All rh. manifestations	..	50	50	Girls more susceptible than boys; pericarditis and mitral stenosis more in females, polyarthritis in males
Musser ²⁵	Females more susceptible at all ages; ratio of 3 to 2 in the first two decades; polyarthritis more common in men, cardiac involvement more common in women
Swift ^{41a}	Polyarthritis more common in men, mitral stenosis and chorea more common in females
Hedley*					

* Since the submission of the paper an article has appeared by O. F. Hedley, (U. S. Pub. Health Rep., 55, 1647, 1940), who has recently shown that 54% of 2539 patients with rheumatic fever admitted to Philadelphia hospitals in the years 1930-34 were females, and that 58% of 3654 patients with rheumatic heart disease admitted to the same hospitals in the same years were females.

Dieuaide¹⁰ is instructive. Of 141 cases of rheumatic fever admitted to the Peiping Union Medical College Hospital from 1921 to 1936, he found that 88 were males; but when this figure was corrected on the basis of the sex distribution of the hospital admissions, the ratio of male to female patients with rheumatic fever was found to be 1 to 1.36. Most observers agree that in children acute rheumatic fever is commoner in the female. Thus, although DeGraff and Lingg⁹ found that 56% of 1633 cases of all ages were males, when these cases were broken down into age groups, females predominated until the age of 13, the sexes were equal between 13 and 28, and there was a male predominance after the age of 28. With reference to the sex incidence in the various rheumatic manifestations, it is seen from Table 2 that polyarthritis is more common in males, while mitral stenosis, pericarditis and chorea are more frequent in females.

In summary, although polyarthritis appears to be more common in the male, the incidence of all rheumatic manifestations is greater in the female, especially in the younger age group. This is in striking contrast to the almost constant ratio of 2 males to 1 female in the reported series of patients with glomerulonephritis.

Comparison of the Preceding Clinical Infection in Acute Glomerulonephritis and Rheumatic Fever. Although the nature of the prodromal infection in acute glomerulonephritis has long been apparent, it remained for Coburn^{6b} in 1931 to point out the significance of the subtle pharyngeal inflammation which precedes the bout of rheumatic fever. This inflammation is classically of a mild variety unlike the predominantly deep type of hemolytic streptococcus upper respiratory infection which precedes the onset of acute glomerulonephritis.

R. F. Loeb^{18b} has summarized the experience of 9 investigators regarding the preceding infection in a total of 943 cases of acute glomerulonephritis. In general, these data show the preponderance of upper respiratory tract infections. Lyttle, *et al.*²² have reported in detail the *type* of hemolytic streptococcus infection which preceded the onset of acute glomerulonephritis in 116 consecutive hospitalized patients, 95 of whom were under 13 years of age. Table 3 shows the prodromal clinical infection in the 104 instances where adequate data were obtained.²²

TABLE 3.—PRODROMAL CLINICAL INFECTION IN ACUTE GLOMERULONEPHRITIS.²²

Infection.	No. of cases.
Mastoiditis	29
Peritonsillar abscess or cervical abscess	15
Cervical lymphadenitis (moderate to severe)	11
Otitis media	8
Sinusitis	1
Acute pharyngitis (most with mild cervical lymphadenitis)	14
Scarlet fever	11
"Common cold"	8
Pneumonia (2 of 3 patients showed hemolytic streptococcus in pharynx)	3
Measles (hemolytic streptococcus in pharynx)	2
Peritonitis (organism unknown)	2
	<hr/> 104

It is apparent that at least 64 of these 104 reported infections can be classified as "deep" rather than "superficial." Since the publication of this series it has been our continued experience that about 2 out of every 3 patients with acute glomerulonephritis will have undergone a "deep" hemolytic streptococcus infection prior to the onset of acute glomerulonephritis.

Peters³² has emphasized the importance of the "septic complication" in the initiation of acute glomerulonephritis. He has stressed the concept that the nephritis does not usually develop in those patients who experience an uncomplicated convalescence following scarlet fever, but rather occurs in those individuals subsequently

affected by "cervical adenitis, sinusitis, otitis media, bronchopneumonia, etc."

Additional evidence showing the importance of "deep" hemolytic streptococcus infection in the initiation of glomerulonephritis is contained in the findings of Musser, Turner and Sodeman.²⁶ These authors have reported 7 cases of typical acute diffuse hemorrhagic nephritis which followed postpartum sepsis. Antenatal examinations in each instance failed to reveal any evidence of renal or vascular disease. The authors state that although the streptococcus was isolated from the uterine secretions in only 1 of the 7 cases, "parametritis and endometritis, both commonly occurring postpartum without localizing signs, may have acted as deep-seated streptococcal infections in the presence of negative cervical cultures." Immunologic tests to detect hemolytic streptococcus invasion were not available.

Futcher¹² has recently reviewed the literature on the occurrence of glomerular nephritis following infections of the skin. It is apparent from the report that various authors have found that from 0 to 28% of the cases of acute glomerulonephritis in their series have followed skin infection. Futcher has added the protocols of 11 patients in whom acute hemorrhagic nephritis followed infected wounds and infections of the skin. Beta hemolytic streptococci were isolated from the cutaneous lesions of 7 of the 11 patients. In 5 of these cases beta hemolytic streptococci were also isolated from the pharynx. In 3 other instances this organism was isolated only from the pharynx.

Although the initiating agent may be similar in rheumatic fever and acute glomerulonephritis, the type of preceding clinical infection differs strikingly in these diseases. In contrast to the "deep" infections occurring prior to the onset of acute glomerulonephritis, the inflammatory process observed in rheumatic fever may be characterized as superficial, slight, or evanescent. The subtlety of the pharyngitis may be such that its detection often escapes many astute observers. Brooks and O'Regan³ observed "catarrhal inflammatory processes" as the most frequent indication of infection prior to the onset of rheumatic fever. These authors also report that cervical or general lymphadenitis occurred in 26.7% of their series of 700 patients with rheumatic fever. The presence of otitis media, mastoiditis, peritonsillar abscess, or cervical abscess are not noted by these workers as precedents of the rheumatism. Coburn^{5a} has stated that "in 100 consecutive cases of rheumatic fever developing in our group we find *none preceded by peritonsillar abscess, one preceded by otitis media, one preceded by mastoiditis, and none preceded by severe cervical lymphadenitis.*" Coburn^{5c} has recently reemphasized the importance of the mild pharyngeal infection in initiating rheumatic fever in his conclusion that "in known rheumatic subjects, suppurative lesions or highly invasive infections do not give rise to acute rheumatism."

Futcher's review and report on the importance of hemolytic streptococcus wound and skin infections in initiating glomerulonephritis has been noted above. These data are of increased interest when compared to the great rarity of such infections as prodromata in rheumatic fever.

In summary, it may be stated that whereas a "deep" hemolytic streptococcus infection precedes the onset of acute glomerulonephritis in about two-thirds of the cases, a superficial, subtle, often barely perceptible pharyngitis is the characteristic prodromal infection in rheumatic fever. It must be stated, however, that the high incidence of deep infection preceding the onset of acute glomerulonephritis may be more apparent than real since patients with severe infections are more frequently hospitalized than are those with mild infections.

Comparison of the Latent Periods Between the Infection and the Onset of Acute Glomerulonephritis, the Exacerbation in Chronic Glomerulonephritis, and the Initial and Subsequent Attacks of Rheumatic Fever. The latent period between infection and the onset of acute glomerulonephritis or exacerbation of the chronic process is difficult to determine accurately unless the patient happens to be under close medical observation during the critical period and frequent urinalyses are being done. However, in many cases the history of the development of the infection and the subsequent onset of hematuria or edema permits a reasonably accurate estimation of the length of the latent period.

Addis¹ finds equal numbers of cases of acute glomerulonephritis occurring during each of the first 3 weeks following infection, with a decreased number in the 4th week. Schick³⁴ and Goodall¹³ find a latent period of 3 to 4 weeks for scarlatinal nephritis, with the maximum incidence falling between the 20th and 22d day. In this connection, the finding of Lyttle^{21b} in scarlet fever is of interest. By means of frequent Addis counts he found that there was an explosive increase in red blood cells, leukocytes, and casts as well as an increase in proteinuria between the 8th and 45th day after the onset of scarlet fever. The modal period was about the 17th day. These urinary abnormalities were unassociated with any of the other manifestations of acute glomerulonephritis. Osman, Close and Carter³¹ report that 80% of post-scarlatinal cases of acute glomerulonephritis develop between the 7th and 16th day. The same authors report a latent period of 3 days or less in only 6 of 37 cases of acute glomerulonephritis following tonsillitis, the mean being 10 days. Winkenwerder, McLeod, and Baker⁴⁸ in a series of 41 cases of acute glomerulonephritis found that only 3 occurred prior to the 4th day after the onset of the infection. The maximum incidence was 11 on the 7th day with an average of 10.9 days for the group. In 7 cases of acute glomerulonephritis following pneumococcus pneumonia³⁶ the latent period varied between 14 and 21 days.

The latent period between the infection and the onset of the exacerbation in chronic glomerulonephritis, however, is greatly shortened. It is almost always 3 days or less, and usually occurs within 24 hours after the onset of infection.^{18,40,48} Table 4 shows the latent period of 28 exacerbations in chronic glomerulonephritis reported by Seegal, *et al.*⁴⁰ Three additional cases have been collected.

TABLE 4.—LENGTH OF LATENT PERIOD BETWEEN INFECTION AND EXACERBATION IN CHRONIC GLOMERULONEPHRITIS.

Latent period in days.	No. of exacerbations.
1	13
2	5
3	2
4	2
7	2
14	1
Unknown	6

Longcope^{19c} has pointed out that "this shortening of the incubation period calls to mind the immediate or accelerated reaction following a second injection of serum." Winkenwerder, McLeod and Baker⁴⁸ have cited a case in which the latent period before acute glomerulonephritis was 13 days, whereas the latent period before a subsequent exacerbation was only 24 hours.

The initial latent (or silent) period between the onset of the infection and the first symptoms or signs of rheumatic fever is generally accepted to be from 14 to 21 days. However, there is no shortening of the latent period before the exacerbation or relapse as compared with the original attack. Coburn^{5a} states, "There is a great tendency for our patients to have the same silent interval with each rheumatic attack. In 20 consecutive cases with two or more attacks there is no difference in the length of the quiescent period occurring in the first attack or in subsequent recrudescence."

The usual latent periods in acute glomerulonephritis and the exacerbations in glomerulonephritis are compared with the latent periods in the initial and subsequent attacks of rheumatic fever in Table 5. It is apparent, therefore, that there is a distinct shortening

TABLE 5.—USUAL LATENT PERIODS BETWEEN THE ONSET OF INFECTION AND THE ACUTE EPISODES OF GLOMERULONEPHRITIS OR RHEUMATIC FEVER.

<i>Glomerulonephritis.</i>		<i>Rheumatic Fever.</i>	
Acute nephritis . . .	7 to 21 days	First attack . . .	14 to 21 days
Exacerbations in chronic nephritis	1 to 4 days	Subsequent attacks .	14 to 21 days

of the latent period preceding an exacerbation of nephritis as compared with that in the original attack. There is no such shortening of the latent period in rheumatic fever. It is possible that this difference is due to the disordered state of the kidney in the one

instance as compared with the temporary healed state existent in the rheumatic subject prior to the recrudescence.

Incidence of Relapse in Acute Glomerulonephritis and Rheumatic Fever. The experience of most clinicians is in agreement with the observations of Atchley and Loeb² and those of Lyttle^{21a} with respect to the fact that patients with *healed* acute glomerulonephritis rarely undergo relapse. None of the large series of patients with *healed* acute glomerulonephritis studied by these workers were later observed to develop the chronic form of Bright's disease.

During clinical investigation of individuals with healed nephritis, bacteriologic studies by Longcope^{19a} and bacteriologic and immunologic investigation by Loeb, *et al.*¹⁶ have shown that patients with *healed* acute glomerulonephritis are extremely resistant to reactivation of the nephritis even in the face of subsequent Group A hemolytic streptococcus infection. In continuation of the study in which 8 cases were described, E. N. Loeb and her associates have observed 8 additional instances of the ineffectiveness of Group A hemolytic streptococcus infection in causing fresh nephritis in individuals in whom a previous acute glomerulonephritis was shown to have healed.

In contrast to the striking resistance of subjects with *healed* acute glomerulonephritis to subsequent attacks of acute nephritis, is the marked susceptibility of individuals with a history of rheumatic fever to repeated bouts of rheumatic fever. Mackie²³ has found that 71% of 393 patients with rheumatic fever had at least one recurrence of the acute disease. He further observed that "only 57 per cent of the first recurrences occurred within four years of the primary attack." Coburn^{5a} has found that "the relapse rate in 100 rheumatic children is more than 80 per cent within five years." It is probable that the rate would be still higher if a longer period of observation were possible.

Longcope^{19c} has commented on this "essential difference" between these diseases and has stated that "complete recovery from rheumatic fever, if this actually occurs, is frequently followed by subsequent acute attacks" whereas "complete recovery from acute hemorrhagic Bright's disease is rarely if ever followed by a second attack."

In summary, it is evident that relapse while a rarity following the healed state of acute glomerulonephritis is a common if not major occurrence following the rheumatic episode.

Comment. The comparison of two such different diseases as glomerulonephritis and rheumatic fever may appear to be of no moment, but from a biologic point of view such a consideration seems of interest. However dissimilar the clinical picture of glomerulonephritis and rheumatic fever, they have one important feature in common: Group A hemolytic streptococcus infection precedes the onset and the exacerbations or relapses in most cases of both diseases.

Certain biologic differences in the natural history of the two diseases have been described above. These are the geographic incidence, the sex incidence, the character of the hemolytic streptococcus infection, the shortening of the latent period in the exacerbation, and the propensity for healing and the persistence of the healed state in acute glomerulonephritis as compared with rheumatic fever. There is no explanation for these differences.

It is possible to postulate that certain strains of hemolytic streptococcus may be "nephritogenic" whereas others may be "rheumatogenic." Even if this were true, all the differences enumerated above could not be explained. In this respect, it is of interest that one of our patients with a history of chronic glomerulonephritis and rheumatic fever subsequently underwent an exacerbation of glomerulonephritis following one Group A hemolytic streptococcus infection and at a later period, a relapse of rheumatic fever following a fresh Group A hemolytic streptococcus infection. Typing of the organisms was not carried out.

The character of the hemolytic streptococcus infection, "deep" in glomerulonephritis and superficial in rheumatic fever, may in part explain the geographic variation in the incidence of the two diseases. Hemolytic streptococcus lymphangitis as a complication of filariasis is frequent in the subtropics and tropics.^{24b} Glomerulonephritis secondary to infections of such a type may help to offset the decreased incidence of nephritis due to the diminished frequency of upper respiratory hemolytic streptococcus infections in the tropics as compared with the temperate zone. Attention has already been directed to the rarity of rheumatic fever following hemolytic streptococcus skin infections. As Futcher¹² has already shown, this type of prodromal infection is not uncommon in acute glomerulonephritis.

Host differences may play the definitive rôle in explaining the biologic differences under consideration. The patient who reacts to hemolytic streptococcus infection with a diffuse inflammatory process in the glomeruli is more apt to be a male than a female and is very likely to have the renal process heal. He is extremely resistant to reactivation of the nephritis once healing has been effected even in the face of subsequent hemolytic streptococcus infections. If chronic glomerulonephritis does develop, exacerbation is subject to a much foreshortened latent period after infection. In these respects nephritic man differs as a host from rheumatic man. These differences are relative, however, since there are a few reported instances of concomitant glomerulonephritis and rheumatic fever in the same individual.

Summary. A limited consideration of certain biologic differences between acute glomerulonephritis, chronic glomerulonephritis and rheumatic fever indicates that:

1. Although both diseases appear to be initiated by Group A hemolytic streptococcus infection, the geographic incidence of acute glomerulonephritis is similar for all latitude regions in North America

whereas the incidence of rheumatic fever is less frequent in the southern than in the northern latitude regions of North America.

2. Although twice as many males as females contract glomerulonephritis, this sex variation is not apparent in rheumatic fever.

3. The preceding clinical infection in acute glomerulonephritis is a "deep" hemolytic streptococcus infection in at least two-thirds of the cases, in contrast to the usual superficial pharyngitis preceding the onset of rheumatic fever.

4. There is a distinct shortening of the latent period following infection in the exacerbation of chronic nephritis as compared with that in acute glomerulonephritis. This shortening of the latent period in exacerbation or relapse is absent in rheumatic fever.

5. Relapse, while a rarity following the healed state of acute glomerulonephritis, is a common if not regular occurrence following the rheumatic episode.

We wish to thank Dr. A. R. Dochez whose point of view led to this study.

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ESOPHAGEAL OBSTRUCTION DUE TO GUMMATA OF ESOPHAGUS AND DIAPHRAGM.

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THOUGH it is known that syphilitic lesions may occur in the esophagus, they are recognized infrequently. In the cases herein reported esophageal obstruction was produced in 1 instance by a gumma situated in the esophagus, and in 3 instances by gummatous lesions of the diaphragm. So far as we are able to determine, syphilitic disease of the diaphragm producing esophageal obstruction has not been recorded heretofore.

Gummatous lesions of the esophagus are known to be exceedingly rare.^{4,6} In 1931, Guyot² made an extensive survey of the literature and accredited Severinus (1580-1656) with the first description of syphilis of the esophagus. Guyot collected 55 case reports of tertiary lesions of the esophagus and added 2 cases of his own. Since 1931 a few additional cases have been reported. Watson-Williams⁷ in 1933 recorded 4 cases of syphilis among 350 patients with dysphagia. The diagnosis of syphilis of the esophagus seems to have been established definitely in 1 instance. The following year, Lukens and Ono³ reported a case of tracheo-esophageal fistula. Necropsy revealed a gumma in the mediastinum involving the trachea and esophagus. Wilcox⁸ reported an instance of syphilis of the esophagus in a female of 25 years. The entire esophagus was involved. Roentgenograms revealed stenosis of the lower two-fifths of the organ. This was relieved by antisiphilitic treatment. In 1936, Avery¹ recorded the case of a white male who had an obstructive esophageal lesion which responded satisfactorily to antisiphilitic

treatment and dilatation. A second patient observed by Avery presented a mid-esophageal lesion which disappeared under anti-syphilitic treatment. The blood Wassermann test was negative, an unusual finding in patients with untreated visceral syphilis. The following instances of syphilitic esophageal obstruction have been observed at the Vanderbilt University Hospital during the past 15 years.

Case Reports. CASE 1.—E. S., white female aged 48, was admitted to the Out-Patient Department on December 30, 1936, because of difficulty in swallowing during the preceding 3 months. She felt that the site of obstruction was under the upper end of the sternum. Regurgitation of solid foods occurred occasionally at first and gradually increased in frequency. For several weeks before admission she experienced difficulty in retaining liquids. Loss of weight and strength ensued. The patient's husband had died of general paresis at Vanderbilt University Hospital 1 year before her admission.



FIG. 1.—Case 1. Esophageal obstruction. Arrow indicates the site with dilatation above this point.

Physical Examination. The patient appeared chronically ill, and except for malnutrition and marked weakness the general physical examination was not remarkable.

Special Examinations. The Wassermann and Kahn tests on the blood were positive. The cerebrospinal fluid was normal.

Roentgenologic examination of the esophagus revealed "almost complete obstruction at about the mid-point of the esophagus with an irregular canalization through the area of obstruction suggesting carcinoma" (Fig. 1).

Esophagoscopy on January 5, 1937, by Dr. Guy Maness, revealed a constriction at about the mid-point of the esophagus. A band of scar tissue was observed in this area, below which there was a granular tumor. The appear-

ance of the latter was suggestive of carcinoma. Microscopic examination of biopsy tissue revealed a chronic inflammatory reaction with no evidence of neoplastic disease.

Course. Beginning January 8, 1937, she was given bismuth salicylate intramuscularly at weekly intervals and potassium iodide thrice daily. After 2 weeks swallowing definitely improved, and after the 4th week of treatment, the taking of food caused very little trouble. On March 5, 1937, after 7 injections of bismuth and 1 of neoarsphenamine, the patient was entirely free of symptoms. A Roentgen ray examination on this date showed an irregular narrowing of the esophagus with some delay in the passage of barium. However, marked improvement since the last examination was apparent. Continuous antisyphilitic treatment was given until she had received 66 injections of bismuth and 50 injections of neoarsphenamine. She gained 25 pounds in weight and was greatly improved. The blood Wassermann and Kahn tests remained positive.



FIG. 2.—Case 1. Slight constriction due to scar is present 2½ years after the institution of antisyphilitic treatment.

Esophagoscopy on June 2, 1937, indicated an increase in the degree of constriction, and consequently dilatation was performed. Subsequently the stricture was dilated 22 times. At the last 7 treatments a No. 45 F olive bougie was easily passed. On December 24, 1937, a Roentgen ray examination showed less obstruction and less dilatation above the point of obstruction than had been observed previously. In May, 1939, a Roentgen ray examination revealed only a slight stricture at the site of the previous obstruction, and a small traction diverticulum (Fig. 2). The patient was last seen in May, 1940, at which time she was entirely free of symptoms.

CASE 2.—J. K., a colored male aged 69, entered Vanderbilt University Hospital November 20, 1925, because of breathlessness, difficulty in swallowing and pain in the abdomen and flanks. These symptoms began about 1 year before admission, their sequence being pain in the region of kidneys, dyspnea on exertion, cough, difficulty in swallowing and abdominal pain after meals. Finally, a short time before admission to the hospital, the patient became bedridden because of weakness. He had lost 45 pounds in weight during the year.

The past history revealed little of interest except that the patient had acquired syphilis at the age of 49.



FIG. 3.—Case 2. Esophageal obstruction at the level of the diaphragm.

Physical Examination. He appeared chronically ill. Dyspnea and orthopnea were present. The veins on the right side of the neck were more prominent than on the left. Substernal dulness was increased but the heart was apparently not enlarged. A systolic murmur was heard over the precordium and over the aortic area. Retraction of the chest wall together with dulness on percussion and distant breath sounds were noted over the region of the upper lobe of the right lung.

Special Examinations. The Wassermann test on the blood was positive. Roentgenologic examination showed fibroid tuberculosis of the lungs. A barium meal was markedly delayed in its passage through the terminal portion of the esophagus. There was moderate dilatation of the esophagus above the lesion, which was thought to be a carcinoma (Fig. 3).

Course. Deep Roentgen ray treatment was given. Within a week regurgitation of food was less troublesome and by December 11, 1925, a

Roentgen ray examination revealed free passage of barium from the esophagus into the stomach. The patient was discharged from the hospital considerably improved. Two months later he was readmitted because of recurrence of dysphagia which began a week after discharge. Dyspnea and orthopnea were marked and he again complained of pain in the kidney regions. The lower anterior portion of the chest was also the site of vague discomfort.

The physical examination on the second admission revealed no new findings. Five days after his second admission to the hospital, he became comatose, and died on the following day.

The clinical diagnoses were carcinoma of the esophagus, fibroid tuberculosis of the lungs, latent syphilis, and bronchopneumonia.

Autopsy. The findings of chief interest were related to the esophagus and were described by the pathologist as follows: "The esophagus is so compressed where it comes through the diaphragm that the lumen is practically closed. The mucosa in this region is white, thickened, almost bloodless, and is thrown into longitudinal furrows which, when the structure is opened, tend to push out into the incision. The muscular coats of the esophagus are also thickened. However, there is no evidence of either inflammation or neoplastic disease of the esophagus. There is simply a constriction of the lumen. The latter is caused by a hard tumor mass in the diaphragm which almost completely encircles the esophagus. A careful dissection reveals that this mass involves the medial portion of the diaphragm including the pillars and the upper medial portion of the liver. The tumor measures approximately 5 x 5 x 6 cm. in size and is nodular. The diaphragmatic muscle surrounding the tumor is markedly fibrosed. Posteriorly the mass extends to the bodies of the first and second lumbar vertebrae, from which it is removed with some difficulty. It extends downward about 1 cm. into the substance of the liver. A sagittal section of the mass reveals a large, irregular, orange-yellow, necrotic fibrous focus about 4 x 5 x 6 cm. in size, which is surrounded by a bluish-white, gristle-like capsule about 1 cm. in thickness. There is no evidence of malignant neoplasm. The entire mass appears to be fibrous tissue with a caseous, necrotic center."

Microscopic examination of the mass revealed chronic inflammatory reaction with caseous necrosis, epithelial cells and fibroblasts. There were occasional foreign-body giant cells. These findings were present both in the portion of the mass attached to the liver and in the portion from the diaphragm proper.

The anatomic diagnosis was "gumma of liver and diaphragm obstructing the esophagus." Additional diagnoses were adhesive pleuritis, fibrosis of the right lung, dilatation of the aortic arch, arteriosclerosis, and focal sclerosis of the myocardium.

CASE 3.—S. S., a colored male aged 56, entered Vanderbilt University Hospital on December 10, 1928, because of the regurgitation of solid food. He stated that for 6 weeks he had noted that solid food would pass "about half-way down" and then would be promptly regurgitated. He had no pain and his appetite had remained good. He had lost about 30 pounds in weight during the present illness.

The past history was essentially negative.

Physical Examination. Nothing remarkable was noted except evidence of recent loss in weight.

Special Examinations. The Wassermann reaction on the blood was positive. A roentgenologic examination with barium revealed an obstruction at the lower end of the esophagus. Marked dilatation of the esophagus was present above the obstruction. The roentgenologist interpreted the findings as being due probably to esophageal spasm.

Esophagoscopy was unsuccessful due to the patient's struggling. Several

hours later a crepitant swelling appeared in the neck. Operation revealed a small tear in the esophagus which was closed without difficulty.

On December 15, 1928, the abdomen was opened. The stomach was markedly atrophic. It was opened in order to facilitate exploration of the lower end of the esophagus. The latter was found to be compressed by a tumor mass in the diaphragm. The mass, which felt smooth and "distinctly doughy," lay to the right of the esophagus and was in intimate contact with the aorta. In view of the positive Wassermann test it was thought that the tumor probably represented a gumma of the diaphragm.

During the first 2 weeks following operation he was fed through a gastrostomy tube and was given 4 injections of neoarsphenamine with the development of a mild arsenical dermatitis. He recovered promptly, and on removal of the gastrostomy tube was able to eat quite satisfactorily. A Roentgen ray examination on January 20, 1929, revealed a "slight constriction, but no obstruction at the lower end of the esophagus." Marked dilatation of the esophagus was still present. He was discharged a week later. On March 11, he returned to the clinic because of the return of dysphagia a few days before. Three injections of bismuth intramuscularly and iodides had been given by his family physician. Dilatation of the esophagus was attempted twice. Only small dilators would pass the obstruction. He returned to the clinic after an absence of 5 weeks. He was entirely free of symptoms and had gained 20 pounds in weight since March 11. A fluoroscopic examination revealed no esophageal obstruction. He was last seen June 18, 1929, after having completed a course of 8 injections of bismuth administered by a private physician. He stated that he felt perfectly well and he experienced no symptoms of esophageal obstruction.

Further information was obtained from the patient's wife in July, 1939. He had died in April, 1937 (8 years after his last visit to the clinic), without receiving further antisymphilitic treatment and without return of dysphagia. Although the exact cause of death could not be ascertained, certainly it was unrelated to the esophagus, since it was stated that he died 2 weeks after an operation for an ulcer of the foot.

CASE 4.—H. C., colored male aged 24, was admitted to the Vanderbilt University Hospital clinic on January 10, 1934, because of difficulty in swallowing of 3 months' duration. At times food would "seem to stop" at the end of the ensiform cartilage and on occasions it would be regurgitated. He had lost approximately 20 pounds in weight.

The past history revealed that he had had a lesion on the penis in 1927 which was treated by 3 intravenous injections.

Physical Examination. Except for evidence of recent loss of weight, there was nothing remarkable.

Special Examinations. Repeated Wassermann and Kahn tests on the blood were positive.

A roentgenologic examination on January 11, 1934, revealed almost complete obstruction at the lower end of the esophagus. The roentgenologist pointed out that the filling defect was rather smooth and suggested that it was due possibly to a gumma (Fig. 4). Esophagoscopy by Dr. Maness revealed marked symmetrical narrowing of the lumen at the line of the diaphragm. There was no ulceration. The mucosa was pale but no scars were seen. It was concluded that the obstruction was due to an extrinsic lesion.

Course. A provisional diagnosis of gummatous syphilis of the diaphragm was made. The patient received 9 injections of bismuth salicylate and 4 injections of neoarsphenamine during the next 8 weeks. Although he then swallowed liquid food without difficulty and gained 20 pounds in weight, solid food continued to produce symptoms and a roentgenologic examination

April 7 was interpreted as indicating almost complete obstruction of the lower end of the esophagus. Attempts at esophagoscopy on April 7 and 14 were unsatisfactory because he coöperated poorly. A silk string was passed for the purpose of subsequently dilating the stricture with a Plummer bag. His temperature rose to 100.8° , he complained of pain in the xiphoid region, and dysphagia increased. Therefore the procedure was discontinued.

On May 16 esophagoscopic examination was repeated. A cicatricial stenosis of the esophagus was encountered at the level of the diaphragm. The mucous membrane was very pale and showed definite scarring. It was impossible to pass flexible bougies completely into the stomach due to resistance of the stricture. To the operator the sensation was that of stricture rather than muscle spasm.

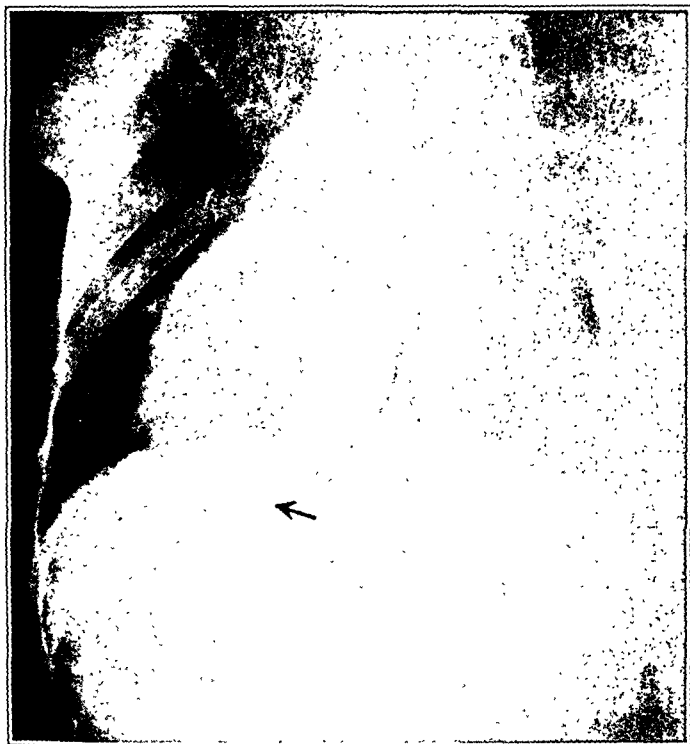


FIG. 4.—Case 4. Esophageal obstruction. The arrow points to the site of obstruction at the diaphragmatic level.

Two weeks later a gastrostomy was performed. Subsequently retrograde dilatation of the stricture was accomplished by bougies inserted through the stomach along a silk string. He was fed through the gastrostomy opening. Antisyphilitic treatment was continued.

On June 26 a No. 22 F. bougie passed the stricture. Treatments were continued and a month later it was possible to pass a No. 40 F. bougie, inserted from above, past the stricture. The passage of bougies of this size was continued at intervals during the remainder of the year. The gastrostomy wound closed satisfactorily.

The patient was seen last on August 20, 1935. During the preceding 14 months he had received 15 injections of neoarsphenamine and 28 injec-

tions of bismuth. In the autumn of 1939 a member of his family stated that he was in excellent health, entirely free of symptoms, and was working in an adjacent state.

Discussion. That esophageal obstruction may occur as the result of gummatous syphilis has been illustrated by the 4 cases herein reported. In 1 instance the tertiary lesion of syphilis was limited to the esophageal wall, whereas in the remaining 3 cases the obstruction was due to gummatous involvement of the diaphragm at or near the esophageal hiatus.

The differentiation of gummatous lesions of the esophagus or diaphragm from obstruction due to carcinoma or cardiospasm can only be made by direct examination (esophagoscopy and biopsy), and the ultimate response to treatment. Antisyphilitic treatment for gummatous lesions producing esophageal obstruction may not only fail to relieve but may actually increase the obstruction ("therapeutic paradox"). Because of resultant fibrosis and contraction of scar tissue esophageal dilatation will probably be necessary.

Case 2 illustrates the importance of accurate diagnosis in esophageal obstruction. The age of the patient and the results of roentgenologic examination led to the diagnosis of carcinoma, and the use of palliative treatment in spite of the fact that he was known to have syphilis. Appropriate treatment at the time the patient was first seen probably would have relieved the obstruction.

Finally it should be emphasized that esophageal obstruction in a case of chronic syphilis may be carcinomatous. Gummatous lesions of the esophagus or diaphragm are rare. Indeed, in individuals with syphilis, the incidence of carcinoma of the esophagus may be greater than obstructive gummatous lesions. This probability has been discussed by Touraine.⁵ Nevertheless, the importance of accurate diagnosis and appropriate treatment is apparent in the light of Case 2.

Summary. Four cases of esophageal obstruction due to gummatous lesions of syphilis have been reported. In 1 case the obstruction was due to a gumma of the esophagus. Gummata of the diaphragm producing esophageal obstruction were present in the remainder. In 3 instances the nature of the lesion was recognized and antisyphilitic treatment and active dilatation of the obstruction offered relief. In 1 case, erroneously diagnosed carcinoma of the esophagus, the patient died without benefit of appropriate treatment.

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SHORT WAVE DIATHERMY IN CHRONIC PROSTATITIS.

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THE frequent reappearance of a patient with prostatitis in the office of the urologist emphasizes the chronicity of the disease and the palliative effect of treatment for this irksome condition. Heat has been of great value to such patients and the opinions of physicians vary as to the method of application. The investigations of Coulter and Osborne^{2a} and Coulter and Carter,¹ show that the electromagnetic field is the most efficient and comfortable method of securing heat in the deeper tissues of the body. We, therefore, decided to investigate the effectiveness of this heating method in the treatment of prostatitis. In addition it was decided to investigate the temperature of the prostate before and after the heat treatment.

In an experimental study on dogs, Schmidt, Beazell and Ivy,¹¹ found that short wave diathermy increased the blood flow of the intestine and colon. Because of the rich blood supply of the prostate it is obviously impossible to perform a satisfactory study of the circulation of that organ. Coulter and Osborne,^{2b} in their study of pelvic heating, found temperatures higher than those procured by other methods. Titus¹³ believes that short wave diathermy is less effective in concentrating energy to the prostate than conventional diathermy. Simpson and Kendell¹² report in a paper on the treatment of gonococcal infection other than arthritis, "Among patients with chronic prostatitis and its complications, 88.8% of the first treated were cured while only 31.5% of the patients in the control group were cured." Elkin and Krusen³ have reported that 2 patients suffering with prostatic abscesses secured a clinical remission when heat localized to the rectum and fever therapy was used in combination.

Methods. Eighty-five patients were diagnosed as chronic prostatitis and were given treatment. The patients varied from 18 to 61 years of age and were divided into 4 groups as shown in Table 1. Grouping of these patients was undertaken so that both duration of the treatment as well as its intensity could be varied. A previous experience had shown us that best results were obtained in these groupings.⁵

Each patient received a genital examination and the urethra was calibrated. A 2-glass urine examination was made; the prostate digitally examined, prostatic secretion expressed and examined for pus and lecithin content, thus establishing the status of the disease.

Treatment was given by means of a pancake coil, enclosed in a bakelite disk and placed underneath the seat of a wooden chair. The disk was connected to an inductotherm. The patient with the necessary clothing

removed sat on the seat of the chair in the usual manner, and the machine setting was placed at a point which we had previously found to give the best clinical results and to produce maximum temperature rise. Each treatment was given for a period of either 20 or 30 minutes as shown in Table 1. Each patient received an average of 10 treatments.

TABLE 1.—DATA ON PATIENTS TREATED.

Group.	No. of patients.	Treatment time (min.).	Age range (years).	Machine setting.
1	26	30	21-56	80
2	24	20	18-61	90
3	17	20	28-52	80
4	18	30	22-58	90

When the patient's treatment was terminated he was instructed to report for reexamination at 3 weeks' and 3 months' intervals when the same procedure of evaluation, just described, was followed.

Posterior urethral temperatures were taken before and after treatment. A special thermocouple made for this purpose was passed to the posterior urethra. Potential differences were read by means of a Leeds & Northrup potentiometer. The thermocouple was calibrated against a standard thermometer and found to have a standard error of plus or minus 0.04° F.

Results. The results of treatment in pus content of the prostatic secretion is shown in Table 2.

TABLE 2.—RESULTS OF TREATMENT ON THE PUS CONTENT OF PROSTATIC SECRETION.

Group.	Before.	After.	Subsequent examinations.	
			Six weeks.	Three months.
1	10-80% Av. 44.1%	24 decreased to 14.9% 2 increased to 80-90%	6 decreased to 5% 1 increased to 40%	3 decreased to 5% 1 increased to 40%
2	10-25% Av. 17.5%	13 decreased to 15% 14 unchanged 6 increased to 30% 1 developed epididymitis	2 decreased to 5%	2 decreased to 5%
3	5-90%	8 decreased 10-70% 1 burn 1 gonorrhea 3 increased 1 fibrous prostatitis unchanged 3 unchanged	5 decreases remained 10-70%	3 decreases remained 10-70%
4	5-90%	15 decreased 5-35% 2 increased 1 unchanged	7 decreases held 2 increased	4 decreases held 1 increase held

Before treatment the pus content of Group 1 varied from 10 to 80% with an average of 44.1%. Under treatment, the pus content of 2 patients was increased from 80 to 90%, but the remainder were reduced at the end of treatment to 14.9%. There was an average rise of 0.6° F. in oral temperature but no appreciable rise in the number of white blood cells. A check in 6 cases was obtained at 6 weeks and 3 cases at 3 months after treatment. In 5 instances the pus content remained at 5%, or lower, while 1 increased to 40% at 3 months. Examination of 1 individual who showed a rise from 80

to 90% revealed a markedly infected maxillary sinus from a cavity of a tooth which had penetrated the sinus. The case which rose to 40% was markedly improved by foreign protein injection (peptone) but returned again to 40% after a course of massage.

Twenty-four cases were treated in Group 2 for 20 minutes at a machine setting of 90, and each patient received an average of 12 treatments. The urinary symptoms, discharge, pain in the back and perineal pain, complained of by this group, were improved or cured in 11 of these patients, while 1 was unchanged. Two urines were cloudy in both glasses, the remainder "clear with shreds and clear." In 1 patient there was no change. Expressed prostatic secretion before treatment varied from 10 to 25% with an average of 17.5%. The white blood cell count of 3 patients was over 10,000, and treatment did not change it. There was an average rise of 0.3° F. in oral temperature and it was noted that men over 40 years showed the highest rise in oral temperature regardless of pus content of the prostate. After treatment 2 patients showed an increase of 30% and 9 patients showed a decrease of 15% in pus content; 1 patient developed an epididymitis. Symptomatically 10 patients were cured or improved and in 1 case there was no change. Six weeks and 3 months checks obtained on 2 patients revealed a less than 5% pus content. One 38-year-old man with an enlarged and tender prostate, arthritic symptoms, premature ejaculations, but with only about a 5% pus content received complete relief; another with no physical findings and only a 10% pus content developed an epididymitis.

In Group 3 treatment was given for 20 minutes with a machine setting at 80. They complained of urinary symptoms, premature ejaculation, backache and of perineal pain. The urine of all was "clear with shreds and clear;" and 5 patients had a white blood cell count of over 10,000. The average oral temperature change in this group was 0.8° F. and the pus content of expressed secretion varied from 5 to 90%. These men received an average of 11 treatments, the longest 14, while 3 patients received 4, 5 and 6 treatments. One of the last 3 patients contracted gonorrhea, 1 had a fibrous prostatitis and when his symptoms were relieved refused further treatment, and the last patient developed a minor burn. Two other patients were considered to have a fibrous rather than a follicular prostatitis. Of the 14 patients who received 10 to 14 treatments, 8 had their pus contents reduced from 70 to 10% in each case. Three were increased and 3 remained unchanged. Another check of 6 patients made 6 weeks later revealed no further pus increase in 5 of the 6 patients examined. Another later check of 3 of these 6 patients showed no further increase.

Eighteen patients were treated in Group 4 for 30 minutes at an intensity setting of 90. They complained of urinary symptoms, of discharge, of sexual symptoms, of back pain and of perineal pain. Four

urines were "cloudy, cloudy"; 1 "cloudy, hazy," and the remainder "clear with shreds and clear." Five patients were found to have white blood cell counts of over 10,000 while the average rise in oral temperature was 0.5° F. The pus content of expressed secretion varied between 5 and 50%. Two patients demonstrated an increase of pus cells under treatment, 1 remained stationary and 15 were decreased from 5 to 35%. A 6 weeks' check of 9 patients showed 2 to have increased while 7 had maintained their decrease. Of 5 patients reporting for reëxamination after 3 months, 4 had maintained their decrease while 1 still showed an increase. One patient developed an epididymitis after 6 treatments, 1 felt fine and dropped out after 5 treatments, while 1 dropped out after 8 treatments. The remainder received from 12 to 15 treatments.

A survey of the entire series of patients revealed that all but 2 so afflicted received relief from their sexual symptoms, 3 noted improvement in their sexual powers. With the exception of 5 patients there was an early response to treatment with moderate to complete relief of all subjective symptoms. The more resistant cases exhibited a moderate exacerbation of subjective symptoms, in part verified by slight fever and leukocytosis which continued into the 5th week of treatment, at which time there was a marked improvement as determined by complete remission of subjective complaints, reduced leukocyte count, lowered temperature, and general appearance of well being. At the end of the series of treatment these patients showed a definitely reduced pus content of expressed secretion and on subsequent reëxamination showed a continued small amount of pus cells with increased lecithin content.

Burns have been known to occur when using the electromagnetic field, and unfortunately, we experienced 2; 1 superficial and the other a third degree burn in the region of the buttocks.

In Table 3 are shown the results of 37 posterior urethral tempera-

TABLE 3.—POSTERIOR URETHRAL TEMPERATURE BEFORE AND AFTER TREATMENT BY INDUCTOTHERM (TEMP. ° F.).

Before.	After.	Before.	After.	Before.	After.
99.2	102.7	99.8	102.3	98.4	101.4
99.7	98.7	100.4	101.9	98.5	103.9
98.4	99.5	99.8	100.8	98.0	100.9
98.6	99.8	100.3	102.0	97.5	100.1
98.6	101.1	99.4	100.2	98.5	100.0
99.2	100.0	99.0	100.1	98.7	100.5
98.2	100.3	99.1	102.0	97.7	99.6
98.5	100.6	100.3	100.6	98.0	101.4
98.8	100.0	99.5	101.5	99.3	101.8
98.8	100.6	99.5	101.2	98.1	99.4
100.5	101.6	99.0	100.9	98.8	100.9
100.3	101.0	99.2	103.0	97.6	100.4
				98.6	101.0
Total average				98.9	100.9
				± 0.14	0.17
Temperature rise				2.0° F.	

tures when using electromagnetic induction. Table 4 gives temperature readings of 6 patients using the Elliott machine applied directly to the prostate and Table 5 gives the temperature rise

TABLE 4.—POSTERIOR URETHRAL TEMPERATURES BEFORE AND AFTER TREATMENT WITH ELLIOTT MACHINE (TEMP. ° F.).

Before.	After.
98.1	99.3
97.5	97.9
97.9	98.3
97.8	98.4
98.4	98.8
98.9	99.1
<hr/>	
Average 98.1	98.6
± 0.22	0.24
Temperature rise . . .	0.5° F.

TABLE 5.—POSTERIOR URETHRAL TEMPERATURE BEFORE AND AFTER TREATMENT BY CONVENTIONAL DIATHERMY.

Before.	After.
97.8	104.4
98.0	105.4
98.4	104.7
98.0	102.6
98.8	102.7
99.2	102.8
98.7	104.2
99.1	102.2
99.6	104.1
<hr/>	
Average 98.6	103.7
$\sigma \pm 0.2$	$\sigma \pm 0.37$
Temperature rise . . .	5.1° F.

secured by means of conventional diathermy applied locally and directly to the prostate by means of a prostatic electrode. Table 6 gives a comparison of three methods, the standard error difference,

TABLE 6.—COMPARATIVE TEMPERATURE MEASUREMENTS IN THE POSTERIOR URETHRA USING VARIOUS HEATING METHODS.

Method.	Treat. time, min.	Temperature, ° F.				Temp. diff.		No. of observ.
		Before.	$\sigma \pm$.	After.	$\sigma \pm$.	Actual.	Diff. $2\sigma \pm$.	
Elliott machine	45	98.1	.22	98.6	.24	0.5	0.64	6
Convent. diathermy	20	98.6	.20	103.7	.37	5.1	0.84	9
Inductotherm	20-30	98.9	.14	100.9	.17	2.0	0.44	37
Control	45	97.6		98.4		0.8		1

and whether or not the differences found were statistically significant. A control was run for a period of 45 minutes. It can be seen by referring to Table 6 that there was no significant rise in tem-

perature when the Elliott machine was used although 45 minutes was given to each treatment. Conventional diathermy localized to the prostate showed the most marked average increase of 5.1° F. The temperature rise secured by the inductotherm averaged 2.0° F.

Discussion. As a result of our investigation it is our impression that inductotherapy is very effective in reducing the subjective symptoms of chronic prostatitis. A majority of the cases revealed a lowered pus cell count in expressed secretion but, unfortunately, we were unable to follow these cases long enough to draw a fair comparison with mechanically accomplished drainage. It is interesting to note that there was no significant temperature rise in the prostatic urethra when the Elliott machine was used, and inasmuch as several reports^{9,10} appeared attesting to its value in the treatment of prostatitis, the question naturally arises as to whether a temperature rise is essential in securing the necessary therapeutic results. That a temperature rise is essential to secure the maximum vasodilatation and blood flow is the most prevalent opinion of the day although this has never been fully established. Johnson, Scupham and Osborne⁶ have shown that there is apparently an optimum temperature for the maximum blood volume change and once this temperature is exceeded there is apparently a decrease in the blood flowing to the part.

Herring,⁴ using conventional diathermy, reported a prostatic urethral temperature of 106° F. and 0.5° F. when using the Elliott machine. He claims that a temperature of the tissues is necessary for a therapeutic result, and that the temperature should range from 105° F. to 106° F.

Mikel and Taube⁸ attributed their successful results secured when using the Elliott machine to the fact that a much greater dosage of heat was possible. They stated it was a more efficient means of applying heat because known temperatures could be maintained. Other methods, they stated, lacked constancy of temperature and control of heat.

Likewise, Lewis⁷ states that the immediate effect of the Elliott machine treatment is a localized pelvic hyperemia and a local elevation of temperature. It would appear from our temperature studies that success of the Elliott treatment cannot be attributed to an increased temperature, and it may well be that an increment of heat is not essential. An increased hyperemia could readily occur as a result of the treatment and this may explain the therapeutic results secured.

Conclusions. 1. Eighty-five patients suffering with chronic prostatitis were each given an average of 10 inductothermy treatments.

2. Inductothermy was effective in reducing the subjective symptoms of chronic prostatitis.

3. Objective findings were improved in a majority of the cases.

4. Posterior urethral temperatures were taken by means of

thermocouples. An average rise of 2° F. was obtained when using the electromagnetic field.

5. The highest posterior urethral temperature was obtained by means of conventional diathermy. There was no significant temperature rise when the Elliott hot-water treatment was given.

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HEAD RETRACTION REFLEX.

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WHEN pyramidal signs, that is, signs of an affection of the upper motor neuron, are found, the next step in examination is to determine the location of the lesion in the long course of the pyramidal cortico-spinal tracts. The pyramidal signs themselves usually do not give any reliable clue to that end. The Babinski sign, for instance, is exactly the same whether the lesion lies in the dorsal spinal cord or in the cortex. However, the history of the case and the motor, sensory and psychic phenomena associated with the disturbance are helpful in localizing the lesion. The problem before us is: how much can we learn regarding the location of the lesion from the behavior of the reflexes alone? This problem arises especially in cases in which the pyramidal tracts are exclusively or predominantly affected, and in which the other tracts and systems are left more or less intact.

The purpose of this article is to draw attention to a reflex which indicates that if a bilateral lesion of the pyramidal tract is present, it is not in the spinal cord but must lie above the upper cervical cord, that is, in or above the brain-stem.

In examining a patient with bilateral pyramidal signs, it is advisable to start with the lower extremities and to proceed upward in an effort to find the highest level at which these signs can still be elicited. The level immediately above this point indicates the location of the lesion. A positive Babinski on both sides indicates that the lesion must lie above the third or fourth lumbar segment.

Marked exaggeration of the knee and adductor jerks with patellar clonus indicates a lesion above the lumbar enlargement. In the area of the trunk, the level of the lesion may be determined from the behavior of the reflexes of the abdominal wall. The neurologic textbooks use chiefly the term, "abdominal reflex,"* and designate it as a "superficial reflex" which consists of contraction of the abdominal muscles with deviation of the umbilicus as a reaction to stroking the skin of the abdomen with a pin, a pinwheel or a similar object. Loss of this abdominal reflex is regarded as an early pyramidal sign and indicates that the lesion lies above D6. This reflex would be more appropriately called an "abdominal *skin* reflex," in contradistinction to the deep reflex of the abdominal muscles which should be called "abdominal *muscle* reflex." In the latter, as in all so-called deep or tendon reflexes, a sudden passive stretching of the muscles themselves provokes their contraction.

The sudden stretching of the abdominal muscles may be brought about by various means. The examiner may place his hand, palm downward, flatly on the patient's abdomen, and tap the dorsum of this hand with a percussion hammer. Or a ruler or muscle plessimeter (such as that devised by Troemner,⁵ which consists of a bayonet-shaped blade and is made of celluloid), may be placed on the abdomen and tapped briskly. The edges of the lower thoracic aperture, the symphysis ossis pubis, the abdominal muscles on the flanks, or other points may be tapped. The best method for eliciting a bilateral abdominal muscle reflex is to place either a limb of the muscle plessimeter or the hand of the examiner obliquely in the middle of the abdomen beneath the umbilicus and to press down so as to stretch the muscles. Tapping the plessimeter or hand with the reflex hammer in a downward direction provokes an additional, brisk stretching of the abdominal muscles and brings forth a massive contraction. This contraction is due to the hypertonicity released by pyramidal involvement. The reflex reaction is often intense and may be accompanied by a reflexive adduction of the legs and, although less frequently, also of the arms. In the presence of pyramidal signs of the lower extremities, loss of both the abdominal skin and the abdominal muscle reflexes indicates a lesion in the dorsal part of the spinal cord below D6. Loss of abdominal skin and exaggeration of abdominal muscle reflex indicates a pyramidal lesion above D6.

Thus, in high situated bilateral pyramidal involvement two pyramidal abdominal signs are observed, namely, loss of the abdominal skin reflex and exaggeration of the abdominal muscle reflex. The exaggeration of the abdominal muscle reflex, which is weak in a normal person, apparently constitutes a more delicate pyramidal sign than the loss of the abdominal skin reflex. I have seen patients

* In his fundamental work on "Neurology" (1940), S. A. K. Wilson⁷ refers throughout to the "Abdominals." R. Brain, in the second edition of his textbook on "Nervous Diseases" (1940), uses the same expression.

with definite bilateral involvement of the pyramidal tract in whom the abdominal muscle reflexes were exaggerated although the abdominal skin reflexes were preserved.

No detailed discussion will be given here on the diagnostically important and fascinating study of the dissociation of the reflexes of the fingers, hands and arms. Suffice it to say that exaggeration of the reflexes and pyramidal signs of the fingers, associated with exaggeration of the triceps reflex and loss of biceps and radial reflexes, clearly indicate a lesion in C5. On the other hand, spastic phenomena of the fingers associated with preservation or exaggeration of the biceps and radial reflexes and loss of the triceps reflex, indicate a lesion in C6-C7. If bilateral spastic phenomena are present throughout the whole arm, the lesion must lie above C5.

Considerable difficulty in topical diagnosis is encountered when, in the presence of a spastic tetraplegia, it must be decided whether the lesion lies in the upper cervical cord, in the brain-stem, or in the brain itself. This difficulty arises because, especially in slight lesions, the pyramidal signs in the area of the neck and face are few and unreliable. The famous Magnus-de Kleijn's neck reflexes, although valuable physiologically, are here seldom of diagnostic significance.

In the area of the face the jaw jerk, which is a purely trigeminal reflex, is usually examined first. Marked exaggeration of this reflex, eventually associated with clonus or trismus, indicates a lesion of the corticopontine tracts above the motor fifth nucleus. It is sometimes difficult to judge whether or not this reflex is exaggerated and it is still harder to draw any definite conclusions from such an exaggeration. This reflex usually is markedly exaggerated in pseudobulbar palsy, but other signs and symptoms of lesions of the corticobulbar tracts are here so apparent that they completely overshadow the exaggeration of the jaw jerk.

In a lesion of the corticopontine tracts of the trigeminus, a positive corneomandibular reflex which consists of a contralateral movement of the lower jaw in a horizontal plane, is occasionally found after pressure has been exerted on one cornea. I have seen this reflex pronounced in amyotrophic lateral sclerosis and in a diffuse pontine lesion, but since it is not always present when it might be expected and is not constant in the same patient, it is of little value in diagnosis.

The much neglected "snout" reflex is useful for the detection of a corticobulbar lesion. On slight tapping of the middle of the upper lip with a percussion hammer, the lips briskly protrude to form a snout. This reflex occurs normally in the newborn during the first days of life. It is often pronounced in severe diffuse brain lesions and in lesions of the cortex and of the corticobulbar tracts, such as encephalomalacia, hydrocephalus, progressive paralysis, pseudobulbar palsy, senile dementia, chronic alcoholism, and other organic

psychoses. Opinions differ as to the significance of this reflex, and its exaggeration is not easily evaluated. However, I am under the impression that a greatly increased snout reflex does indicate to some degree the involvement of the corticobulbar pathways.

Once, on examining a patient with amyotrophic lateral sclerosis for this snout reflex by tapping the middle of the upper lip with a percussion hammer, I observed that this reflex was not pronounced but that every time the upper lip was struck with the hammer, a reflex movement, consisting of a brisk, quick, involuntary backward jerk of the head, took place. This movement occurred even when the patient lay on his stomach with the head hanging freely over the edge of the table. In this position the reflexive retraction took place against the weight of the head. A careful analysis of this reflex showed that the muscles in the nape of the neck retracted the head; in other words, this was a true *head retraction reflex*. As is the case in all so-called deep or tendon reflexes, this retraction of the head always follows a quick stretching of the muscles. The stretching of these muscles takes place when the tap of the hammer on the jaw provokes a sudden bending of the head to which head retraction is a reflexive answer. The muscles in the nape of the neck respond to stretching with a reflexive contraction in the same way as the quadriceps muscle does when it is longitudinally stretched by a blow on the patellar tendon.

The head retraction reflex may be elicited in different ways all of which cause a sudden bending of the head. The root of the nose may be tapped with the percussion hammer in a downward direction, or the middle of the upper lip may be tapped; or the patient may clench his teeth tightly and be given a tap on the chin downward. The reflex may sometimes be elicited by tapping the middle of the occipital bone upward and forward. However, the best method appears to be the tapping of the upper lip. The intensity of the reflexive response depends on the force of the tap, its direction, and the length of the lever on which the blow acts to cause the rotation of the head through a transverse axis. The reflex is most difficult to elicit by striking the nape of the neck upward because the lever on which the blow acts to bring about a bending of the head is too short.

The best way to observe the reflexive movement of the head is to sit beside the patient at his right side while the light is on his left. For the elicitation of the head retraction reflex, as for that of the other deep reflexes, all the muscles concerned must be relaxed. At first this may be difficult to achieve, and it is astonishing to see how tensely many patients hold their neck muscles. In an examination for the presence of the head retraction reflex, all the different maneuvers for the reinforcement of the knee jerk may be applied: the maneuver of Jendrassik may be used; the patient may be instructed to grasp the arm of the examiner, to squeeze his own

thighs, to cough, to take a deep breath, to gaze at one point; or other means of diverting his attention may be employed. On the other hand, some degree of tension of the head retractors is favorable for the appearance of this reflex. It is, therefore, essential before eliciting the reflex to ask the patient to keep his head bent forward slightly and loosely, or even to make a very slight movement of the head backward.

The head retraction reflex has never been found strongly positive in normal persons even though other tendon reflexes were exaggerated. Nor has it been found positive in hemiplegia or in unilateral ascending spastic paralysis (Mills-Spiller's disease). In these conditions the tapping of the face does not produce a reflexive stretching of the head, but merely a slight vibration. In some instances this mechanical vibration of the head is hard to distinguish from a slight retractive movement. Under favorable conditions this reflex, as every other deep muscle reflex, may possibly be elicited in a normal person. In organic lesions the reflexive head retraction is usually so outspoken that its pathologic significance can hardly be doubted. However, occasional borderline or doubtful reflex conditions are seen.

This reflex has never been found positive in a purely spinal affection. Lesions of the medulla oblongata affecting exclusively the nuclei and sparing the pyramidal tract, such as progressive bulbar palsy, never give a positive head retraction reflex.

This reflex is most pronounced in amyotrophic lateral sclerosis and has also been elicited in lateral sclerosis, cerebrospinal lues, and arteriosclerotic and other diffuse lesions of the brain including essential hypertension. It has likewise been noted in dorsolateral sclerosis and in multiple sclerosis. In advanced cases of amyotrophic lateral sclerosis with bulbar involvement, this reflex is so pronounced that the slightest tapping of the face, even with the finger, produces a brisk jerk of the head backward. The reflex was negative in a patient with amyotrophic lateral sclerosis in whom a flaccid paralysis of the head retractors caused the head to fall forward. Furthermore, it was negative in a patient with the lumbar type of amyotrophic lateral sclerosis in whom the degeneration slowly crept upward and the upper extremities were only slightly affected.

The results of recent research on the pathology of amyotrophic lateral sclerosis explain why the head retraction reflex is strongly positive in this disease. Since the degeneration of the pyramidal tracts can be traced upward from the spinal cord to the cerebral cortex, it is apparent that amyotrophic lateral sclerosis is not only a spinal disease affecting the pyramidal tracts in the lateral columns of the spinal cord, but also an affection of the brain. It really is not an amyotrophic *lateral* sclerosis but an amyotrophic *pyramidal* sclerosis. Furthermore, the frontal and temporal cortices may be affected and may cause the appearance of psychic and organic

cerebral phenomena. The occurrence of the head retraction reflex in all diffuse cerebral lesions is easily explained by their effect on the widespread corticobulbar tracts.

It is remarkable that the head retraction reflex may be positive in dorsolateral sclerosis. In accordance with the findings of recent years, focal signs of degeneration in the white matter and in the ganglion cells of the cortex, similar to those of the spinal cord, may occur in dorsolateral sclerosis. In multiple sclerosis the head retraction reflex is positive only in cases of definite involvement of the brain; it is absent in the purely spinal forms.

The practical importance of this reflex lies in the fact that in some cases it has been the only sign and in others the outstanding objective sign of a supracervical or a suprapontine lesion. Some lesions apparently spinal are not exclusively spinal, but have crept beyond the spinal cord and have affected the corticobulbar tracts. In some cases the positive head retraction reflex is a very helpful diagnostic adjuvant in confirming other findings. In certain remarkable cases, the unexpectedly positive head retraction reflex was the first sign to direct attention to a supracervical lesion, the diagnosis of which was confirmed later by other means. One patient especially impressed me. He was a 60-year-old gardener who complained of weakness of the left leg of several months' duration. At first glance, his gait and his history (he had been working for 16 years as a gardener and had frequently assumed the squatting position) gave the impression that he had an occupational peroneal palsy. But the head retraction reflex was strongly positive and a detailed examination revealed other signs of an amyotrophic lateral sclerosis. It was of the ascending lumbar type, and the head retraction reflex was the only sign to indicate how far upward the involvement of the cerebrospinal axis had extended.

The head retraction reflex may facilitate the differential diagnosis of high cervical cord lesions and systemic degenerations of the spinal cord, such as amyotrophic lateral sclerosis and dorsolateral sclerosis. Various investigators have recently shown how difficult such differential diagnosis may be and how easily even an experienced neurologist may be misled.^{2,4} Since systemic degeneration may in the long run affect the supranuclear bulbar tracts and thus produce a positive head retraction reflex, and since this is not to be found in a lesion confined to the high cervical cord, the presence or absence of the head retraction reflex may play a decisive rôle in the differential diagnosis of these affections and eventually may obviate the use of myelography. In one patient in whom a protruded intervertebral disk was suspected and myelography was performed, a strongly positive head retraction reflex indicated clearly that the lesion extended beyond the spinal cord. Further examination proved the case to be one of genuine lateral sclerosis.

This reflex can give invaluable aid in the differential diagnosis

of amyotrophic lateral sclerosis which is sometimes difficult because the Babinski reflex is often absent in this disease. In a patient with a clinical picture of progressive spinal muscular atrophy, a positive head retraction reflex indicates the presence of amyotrophic lateral sclerosis. Furthermore, this reflex is of value in the differential diagnosis of all the conditions accompanied by tetraplegia, such as systemic degenerations (*e. g.*, Charcot-Marie-Tooth disease), cervical myelitis, spinal vascular diseases, tumors, pachymeningitis cervicalis hypertrophica, and polyneuritis. In such differential diagnosis, the behavior of the reflex indicates whether or not the lesion has transgressed the boundaries of the spinal cord. In systemic degeneration of the spinal cord, a positive head retraction reflex indicates extension of the lesion to the brain and so becomes a valuable prognostic sign.

A cerebral lesion involving the leg center, the lobulus paracentralis bilaterally, such as may be due to a parasagittal meningioma, tangential gunshot wound or other traumatic injury of the top of the skull, thrombosis of the superior longitudinal sinus, or Little's disease, may produce a spastic paraplegia of the lower extremities without interfering with the corticobulbar and corticospinal tracts leading to the upper extremities and to the head and face. In such a case, spastic phenomena of the lower extremities would be expected but the head retraction reflex would be negative. I observed only one patient in whom a parasagittal meningioma could be suspected; but the diagnosis was not conclusive. Here may be a further possibility for the utilization of the head retraction reflex.

No patient with meningitis, basilar or other type, has been examined for this reflex that may be present here even in the early stages of the disease. At the beginning of the meningitis, the actual retraction of the head may not be marked; however, muscular resistance and pain may be elicited if an attempt is made to flex the head forward. These conditions favor the appearance of a positive head retraction reflex.

Because of limited experience and lack of pathologic material, no conclusions as to the exact location of the paths of this reflex can be drawn from purely clinical observations. However, it seems certain that a release of cortical inhibition must take place in the muscles that retract the head before this reflex could appear. Therefore the lesion must lie bilaterally on the corticospinal tracts above the anterior motor nuclei of the upper cervical segments. Its exact location is not essential, but it usually lies in the upper rather than in the lower parts of these tracts.

Since the afferent limb of the arc for the head retraction reflex goes through the trigeminal nerve, this reflex must be negative in bilateral trigeminal anesthesia even if a bilateral supranuclear lesion is present. Thus far I have not had an opportunity to examine a patient with such a condition.

Some hypertonia of the head retraction muscles, that is, some kind of latent opisthotonos, is a condition *sine qua non* for the appearance of this reflex. However, a real opisthotonos has never been found in patients with a positive head retraction reflex, and the expected hypertonia of the neck muscles, even in patients with a marked head retraction reflex, has been slight if at all demonstrable.

Marked retraction of the head, together with pronation of the upper and inversion of the lower limbs, is characteristic of the decerebrate rigidity due usually to an interference with the motor centrifugal tracts at the level of the mesencephalon. The head retraction reflex may belong to the syndrome of decerebrate rigidity, since a mild degree of hypertonia of the head retraction muscles is necessary for its appearance and this hypertonia and opisthotonos are among the cardinal signs of decerebrate rigidity. Thus the head retraction reflex would be an expression of the mildest subclinical form of decerebrate rigidity.

I have been unable to find any reference to the reflex phenomenon described herein in the popular English, French and German textbooks on neurology or neurologic diagnosis. Foerster,¹ in the chapter on exaggeration of the reflexes in the domain of the cranial nerves, of his monograph "Motor Areas and Tracts," discussing the behavior of the periosteal reflexes of the face, stated that when the corticobulbar tracts are eliminated "wherever the stimulus may reach the skull or the face, the whole musculature of the face contracts more or less, not only on the stimulated side but also on the contralateral side. Not infrequently the extensors of the head take part in this reflex action in such a way that the head makes a jerk backward."

In his recent work, Wilson⁷ notes in the chapter on amyotrophic lateral sclerosis: "In some spastic spinobulbar cases I have found that downward percussion on the chin (mouth shut) provoked contraction of head extensors (deep posterior rotators); so far as is known to me this reflex of upper cervical segments has not hitherto been described." Even Wilson, who had an astounding knowledge of current literature and who cited in this chapter works that appeared in 1932, had overlooked an article on this subject by Nemlicher *et al.*³ published in 1931. In pseudobulbar palsy, in amyotrophic lateral sclerosis and in bilateral hemiplegia these authors observed a reflex corresponding to the head retraction reflex. They called it medio-facial or faciocervical and considered it a periosteal reflex. They regarded it as pathognomonic for bilateral affections of high location in the pyramidal tracts.

The observation of Weingrow,⁶ according to which tapping of the zygomatic or nasal region of the face causes contraction of the facial musculature and a slight movement of the head (the latter due to contraction of the cervical musculature), apparently belongs in the category of this reflex.

The head retraction reflex is so striking that it must also have been observed and described elsewhere. It is noteworthy that this reflex has now been described independently by five authors, three of whom did not refer to the work of the others.

Summary. In bilateral pyramidal lesions situated above the highest cervical cord, tapping of the face brings forth a reflexive retraction by provoking a sudden bending of the head. This head retraction reflex constitutes a reliable sign of bilateral supracervical involvement of the pyramidal tract which may be of importance in the diagnosis of these conditions and in their differentiation from purely spinal affections. Preliminary experiences with this reflex arouse many questions and warrant the suggestion that it be studied further.

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THE URINARY EXCRETION OF BISULFITE BINDING SUBSTANCES BY HUMAN ADULTS ON THIAMIN-LOW DIETS.*

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It is generally accepted today that pyruvic acid is not metabolized properly in the animal body in thiamin deficiency and so may accumulate in abnormal amounts.^{14, 20} Clift and Cook⁵ utilized the property common to keto acids and aldehydes of combining with bisulfite under certain conditions in a method for the determination of pyruvic acid. In biologic fluids it measures other

* From the thesis presented by Maurice E. Shils to the faculty of the School of Hygiene and Public Health, The Johns Hopkins University, in partial fulfillment of the requirements for the degree of Doctor of Science in Hygiene.

substances in addition to pyruvic acid—the total determined being called the bisulfite binding substances (B.B.S.). Although not specific for pyruvic acid, the method is of value under controlled conditions and has the advantage of being simple and rapid.

Thompson and Johnson²⁰ were the first to attempt to correlate pyruvic acid and B.B.S. concentrations in the blood of thiamin-deficient animals. Deficient rats and pigeons had a greatly elevated B.B.S. and pyruvic acid content; quantitative estimations showed the rise in B.B.S. to be due entirely to the increase in pyruvic acid. Since then, in keeping with the importance of the subject, a number of papers dealing with human and animal experiments have appeared and are reviewed rather fully by Platt and Lu.¹⁴

These workers measured pyruvic acid and B.B.S. in the blood and cerebrospinal fluid of beriberi patients. The values for pyruvic acid and B.B.S. in subacute cases were within normal limits or only slightly raised, while in acute cases the increases were quite marked with a decrease occurring quickly following thiamin injection. Taylor, Weiss and Wilkins¹⁹ have found increased blood B.B.S. in untreated human thiamin deficiency as well as in a number of other unrelated conditions. Consequently, an increased B.B.S. value does not necessarily indicate thiamin deficiency. This, in itself, does not eliminate the possibility of using the level of B.B.S. as a measure of thiamin deficiency. Logically, a high level of B.B.S. not caused by thiamin deficiency should remain unchanged on administration of the vitamin, whereas the high B.B.S. caused by the accumulation of pyruvic acid as a result of the vitamin deficiency should quickly decrease. A suitable procedure would seem to include the determination of B.B.S. before and after the ingestion or injection of a standard dose of thiamin.

Evidence was therefore sought concerning the behavior of B.B.S. in experimental human deficiency. Urine, in preference to blood, was analyzed for its B.B.S. content. At the time these studies were made values had not been reported for B.B.S. in urine. Since then Banerji and Harris² have reported data on B.B.S. in the urine of men subsisting voluntarily on a thiamin-low diet. Their results differ from those reported here.

Experimental Methods. *Determination of B.B.S. in Human Urine.* The principle of the Clift and Cook procedure⁵ is as follows: pyruvic acid forms an addition compound with sodium bisulfite in acid medium. Excess bisulfite is removed with iodine and the bound bisulfite is liberated by the addition of alkali. Standard iodine solution is used to measure the liberated bisulfite.

Preliminary investigation indicated that this procedure cannot be applied directly to urine. The primary obstacle is the presence in urine of reducing substances whose reducing action is greater the higher the pH. These interfering substances often reduce more iodine than the bisulfite liberated in the determination, resulting in very high values and in a poor final end point. Since the interference is very much less at the lower pH where the bisulfite addition compound is formed, efforts were made to determine the

B.B.S. by measuring the excess uncombined bisulfite by titration with standard iodine solution as was done by Ripper in his method for the determination of acetaldehyde.¹⁵ The variable results obtained through volatilization and oxidation by air of the bisulfite caused this procedure to be abandoned.

It was found that 1 mg. of uric acid reduced about 1.5 ml. N/200 iodine solution. Uric acid and some other compounds found normally in urine can account for an appreciable amount of iodine reduction unless means are employed to prevent their interference.

Precipitation by means of phosphotungstic acid and lead acetate proved unsatisfactory because pyruvic acid added to urine which was then subjected to the treatment no longer could be found as B.B.S.

Adsorption of the interfering substances from urine with Lloyd's reagent (Lilly), a hydrated aluminum silicate, followed by permutit, proved more successful. Folin and Svedberg⁷ in the determination of sugar used these adsorbents to remove reducing substances. Pyruvic acid is not adsorbed from an aqueous solution and can be recovered quantitatively. Pyruvic acid added to urine which is then put through the adsorption procedure is not destroyed. By this procedure most of the reducing substances are removed, the final end point is much more definite, no frothing occurs, and the urine is clear.

To eliminate the necessity of adsorption with permutit the modification of Hamilton⁸ was adopted, whereby acid-treated Lloyd's reagent alone is used. Continuous mechanical mixing of the reagent in the acids shortened the period of preparation. The final washed and dried product was powdered and put through a 40-mesh screen. It was found that this acid-washed adsorbent contained a small quantity of B.B.S. which differed in amount from batch to batch. It was necessary, therefore, to find the blank for each batch. The pH for the dissociation of the pyruvic acid bisulfite compound is about pH 6.0.

The procedure adopted for determining B.B.S. in human urine is as follows: The 24-hour output collected under toluene is diluted to 1500 ml. if below that volume. To 100 ml. of this dilute urine are added 40 ml. 0.125 N oxalic acid and then 32 gm. of the acid-washed Lloyd's reagent. After shaking 4 to 5 minutes the adsorbent is allowed to settle out and the urine is filtered through No. 50 Whatman filter paper (B.B.S. free). Twenty-five ml. aliquots are taken and to each is added 0.6 ml. of approximately 1 M sodium bisulfite solution. After standing 15 minutes at a temperature below 25° C., 1 ml. of 1% starch solution is added. The excess bisulfite is removed with 0.1 N iodine and 1 to 2 drops more iodine are added and allowed to remain for about 3 minutes. The solution is then decolorized with approximately 0.01 N sodium thiosulfate, after which N/200 iodine solution is added to a faint blue. After swirling has stopped, 5.5 ml. of a clear saturated solution of sodium bicarbonate are run in down the sides of the flask to liberate the bisulfite. Two-hundredth N iodine solution is added dropwise from a microburette at a constant rate until a faint blue color persists throughout the solution for a few seconds. This is the final end point.

The differences between the 25 ml. aliquots of a sample done in triplicate usually fell within 0.2 ml. of each other and rarely differed by more than 0.3 ml., as verified by many determinations. Twenty-five ml. aliquots of urine from 4 individuals eating approximately the same kinds of food gave average values between 1.5 and 2.3 ml. N/200 iodine solution.

Since it is quite certain that other substances than pyruvic acid contribute to the B.B.S. of normal and deficient individuals, we prefer to express results in ml. N/200 iodine solution instead of as "pyruvic acid," as has been done by other workers.

Production of Thiamin Deficiency. Two normal young men (A and B) and 2 normal young women (C and D) limited themselves to a diet low in thiamin, but otherwise regarded as adequate as respects essential nutrients. The diets were as follows:

- Breakfast:* Cereal: unfortified farina or white rice
Pancakes of white flour and egg white with corn syrup
(taken by A and C)
White bread or soda crackers with butter
- Lunch:* Small serving of cheese, American or Swiss
Soda crackers or white bread
Cooked polished rice with cream (occasionally)
Coffee
Milk (one glass by A for first 3 weeks)
Apple (by A and C)
- Dinner:* Choice of cooked hominy, macaroni, polished rice or spaghetti
Small piece of beef (once weekly by B and D)
White bread and butter
Jello
Coffee or tea

Each subject took a daily supplement of: *a*, salt mixture to supply calcium, iron and magnesium; *b*, acid washed casein, 15 gm.; *c*, autoclaved yeast to supply B complex other than thiamin, 15 gm.; *d*, ascorbic acid, 30 mg.; *e*, vitamins A and D as cod-liver or percomorph oil.

A liberal estimation of the daily thiamin intake calculated from the data taken from two sources^{3,23} placed the value at 150 to 180 micrograms for each subject. The daily adult requirements are estimated at 700 to 1000 micrograms.²³ The experimental diets were, therefore, quite low in thiamin. The thiamin:non-fat calory ratio was estimated at no more than 0.12. Diets with a ratio of less than 0.3 are beriberi-producing.²³

The 2 male subjects restricted themselves to the thiamin-low diet for two periods, once in February and again in June and July of 1939. The first deficiency period lasted 14 days; the deficient diet was continued 3 days more with each individual receiving 5 mg. of crystalline thiamin* daily. In the second period both male subjects and the 2 young women were supplemented with 1 mg. of thiamin for 2 days after beginning the deficient diet. Individual A continued on the deficient diet for 37 days more. On the 38th day 1 mg. of thiamin was injected intravenously for a tolerance test^{13†} and the

* The thiamin was a gift of Merck & Co., Inc.

† The measurements of thiamin and the thiamin tolerance test were made by Dr. Victor Najjar of the Harriet Lane Home, Johns Hopkins Hospital. The thiamin was determined by the thiochrome method of Hennessy and Cerecedo.⁹

diet was continued for 2 days more supplemented with 5 mg. of thiamin per day. Individual B consumed the deficient diet without any thiamin supplement for 29 days, received 1 mg. thiamin for the tolerance test on the 30th day and continued on the deficient diet with 5 mg. daily for 5 days more. Individual C ate the deficient diet for 14 days after the 2-day thiamin supplement and then received 5 mg. thiamin for 3 days more. Individual D consumed the deficient diet for 19 days, after which thiamin was given for 2 days.

B.B.S. determinations were made every other day except for the first and last week of each subject's period when they were made every day.

Results. Definite evidence for the low-thiamin intake of the subjects is given by the results (Table 1) of the determinations of thiamin excretion for individuals A and B in the second experiment.

TABLE 1.—EXCRETION OF THIAMIN PER 24 HOURS (IN MICROGRAMS).

	Day on deficient diet.										
	24.	25.	26.	27.	28.	29.	31.	33.	35.	36.	37.
Subject A	7.4	0.0	0.0	0.0	0.0	3.8	3.8	11.9	15.0	0.0	0.0
Subject B		3.0	3.0	2.7	3.0						

The range of excretion on a normal diet is usually over 100 micrograms per 24 hours.¹³

Physical examinations of subjects A and B just before the injection of thiamin indicated that both individuals were clinically normal. Electrocardiograms taken before and at the end of the experimental diet were normal.* No symptoms definitely ascribable to the deficiency were noted at any time. The monotony of the dietary schedule caused loss of appetite, and occasional periods of fatigue were experienced by the subjects, but these symptoms could not be ascribed to the lack of the vitamin, since they persisted after thiamin administration.

Further evidence of the low intake of thiamin was afforded by the thiamin tolerance test of Najjar and Holt¹³ which was given to subjects A and B at the end of their second experiment. It was repeated after both individuals had been on a normal diet for more than a month. The results are given in Table 2.

TABLE 2.—THIAMIN TOLERANCE TEST GIVEN TO INDIVIDUALS ON THIAMIN DEFICIENT AND NORMAL DIETS.

(Thiamin excretion in micrograms after intravenous injection of 1 mg. thiamin.)

Time after injection (hours).	A—On deficient diet July 10 (38th day).	A—On normal diet August 20	B—On deficient diet July 2 (30th day).	B—On normal diet September 28.
$\frac{1}{2}$	58.0	208.0	74.5	211.2
1	0.7	12.4	3.1	17.2
2	1.5	16.8	0.0	8.6
3	Trace	8.1	0.0	6.0
4	0.1	...	0.0	4.6

* The electrocardiograms were made by Dr. Anna Baetjer of the Department of Physiological Hygiene, School of Hygiene and Public Health.

These figures indicate¹³ a low intake of thiamin and a need of the body for the vitamin. The degree of retention as shown by the excretion before and after a diet with adequate thiamin is striking.

There was no significant rise in the B.B.S. of any individual during the course of the deficiency, nor was there any change on administration of thiamin. Since the results in the two periods were the same, only data from the second experiment is given in Table 3.

TABLE 3.—B.B.S. IN URINE OF SUBJECTS ON THIAMIN-LOW DIET.
(Per 24 hours in ml. N/200 iodine.)

Day.	Subject A.	Subject B.	Subject C.	Subject D.
1	157	172	134	168
10	128	167	124	182
13	119	157	142	142
15	133	157	136*	134
16	128	144	141*	154
19	115	174	...	142*
20	119	188	...	152*
30	143	146*		
31	133	137*		
38	134*			
39	147*			

* Thiamin administered.

Table 3 indicates a marked fluctuation in the values but all are within the same range. The extreme range of values of A for all the 32 determinations made was 115 to 180 ml. N/200 iodine; of B for 27 determinations 137 to 200 ml. Since the daily fluctuations could be caused only partly by measuring variations (20 ml. maximum) other factors enter, chief among them being probably daily variation in the quantity of food, which did occur. It has been found with rats¹⁸ that the quantity of food intake has a decided influence on B.B.S. values.

Discussion. The results reported here indicate that 29 to 37 days on a thiamin-low diet such as used in these experiments are not long enough for a significant disturbance in intermediary carbohydrate metabolism of normal young adults, if the level of B.B.S. in urine is taken as a criterion.

On the other hand, Banerji and Harris² mention briefly that in the urines of 3 individuals on an experimental beriberi-producing diet, the B.B.S. increased three to four times over the initial values in about 1 week. Experience with rats^{2,18} indicates that within 2 weeks after being placed on a thiamin-deficient diet, the urinary B.B.S. increases greatly. The report of Banerji and Harris² would indicate a similar rapid disturbance in the metabolism of human beings—a finding not substantiated by our observations. The analytic procedure used for human urine is not given in detail by the English workers, but it probably differs from our procedure because the normal B.B.S. (expressed as mg. pyruvic acid) found by them is 140 to 190 mg. per day, whereas the highest value found by us was 63 mg. The difference may be due to the fact that we

removed interfering substances by adsorption. Further proof that the adsorption treatment does not remove pyruvic acid is given by the results with rats where the same procedure was applied.¹⁸

Perhaps if the deficiency period was extended, increased values for B.B.S. may have occurred.

Comparison with the reports of blood B.B.S. estimations is interesting. Williams, Mason and Smith²² carried experimental thiamin deficiency to a period of 21 weeks in 4 patients without detecting any elevation in the B.B.S. of blood. Robinson, Melnick and Field¹⁶ found no elevation of blood B.B.S. during a 22-day period of low thiamin intake. Elsom *et al.*⁶ reporting a case of experimental human B-complex deficiency found no rise in either blood pyruvic acid or B.B.S. in the fasting state during 9 weeks without thiamin. The work of Platt and Lu¹⁴ indicated little or no increase in blood pyruvic acid or B.B.S. in subacute beriberi.

Inability to find increased B.B.S. values in the blood in individuals on thiamin-low diets where symptoms of the deficiency have appeared^{16,22} raises an interesting problem. Several possible explanations present themselves. A. The renal threshold for pyruvic acid and B.B.S. may be about the level normally existing. The first evidence of deranged carbohydrate metabolism would then be expected to be found in urine. In this case the B.B.S. or pyruvic acid would rise in the blood only in chronic or severe deficiency when the kidneys were unable to keep the blood level normal. A comparison of the blood and urinary levels of pyruvic acid or B.B.S. at the same time in controlled experiments would help answer this question. Sherman and Elvehjem¹⁷ have found that in thiamin-deficient chicks while the blood B.B.S. level was normal, the B.B.S. value of the excreta (chiefly through the urinary component) was increased threefold. B. If the B.B.S. and pyruvic acid renal threshold in humans is not at the normal level for the blood, then deficiency symptoms may appear with very little, if any, increases in the blood and urinary concentration of these substances.

High values for B.B.S. in blood have been reported in pellagrins^{11,12} which decreased upon injection of cocarboxylase with remission of neurologic symptoms; in pregnancy,^{2,4} in beriberi¹⁴ and in inebriation,²⁴ all being conditions associated with chronic malnutrition. However, there are also reports of cases of chronic thiamin deficiency where there was no rise in blood B.B.S.^{14,16} The blood B.B.S. level would thus seem to be an unreliable index of thiamin nutrition. Increased blood pyruvic acid concentration has been found in the above conditions^{4,14,24} as well as subnormal thiamin excretion.^{13,16}

There are reports in the literature of increased blood pyruvic acid concentration^{6,14} with no concomitant increase in B.B.S. This is difficult to understand because it is well established^{5,14,17,20} that pyruvic acid binds bisulfite under the conditions of the Clift and Cook procedure.⁵

The literature concerned with the appearance of symptoms in experimental human deficiency is also not in agreement. No symptoms attributable to thiamin deficiency were found in the experiments described here. Likewise, Wang and Yudkin²¹ report no objective symptoms in 3 volunteers on a diet low in thiamin (100 to 150 micrograms daily) after 10 to 14 days.

Alvarez *et al.*¹ noted no symptoms in 3 individuals on a low-thiamin diet for 6 weeks. Williams and coworkers²² found symptoms, but as they state, "the onset of these symptoms was much later than had been anticipated." (Evidently from the report of Jolliffe *et al.*¹⁰).

Other workers have found symptoms occurring rather soon after restriction to the deficient diet. Jolliffe and coworkers¹⁰ found symptoms in 4 out of 5 subjects, with the first showing objective signs as early as the 5th day. The addition of thiamin to the thiamin-low diet caused all symptoms to disappear within 3 days. The deficient diet contained more thiamin than any other discussed here (474 micrograms daily). Indeed, Wang and Yudkin²¹ have recalculated the thiamin content of the diet used by Jolliffe *et al.*¹⁰ according to the tables of Fixsen and Roscoe³ and have found it to contain 750 to 1000 micrograms, which is within the range of normal requirement.

Robinson, Melnick and Field¹⁶ observed aching of the calf muscles after exercise as early as the 12th day on a deficient diet, which increased as the diet continued. Paresthesias of the lower extremities and dyspnea on mild exertion also occurred before 22 days. There were no changes in the electrocardiogram. Elsom *et al.*⁶ found clinical manifestations and metabolic changes evident only after 5 weeks on the experimental diet which was deficient in the whole B complex.

These divergent results may possibly be explained by the facts that: *a*, individuals differ in their requirements for the vitamin; *b*, the tables of the thiamin content of foods are admittedly far from exact and thus accurate calculation is impossible; or, *c*, conditions of experiments in the several laboratories varied considerably.

On one point all papers,^{13,16,21,22} including this one, dealing with thiamin excretion agree. All relate a decrease during the deficiency period. It is interesting to note that Banerji and Harris² report increased urinary B.B.S. values in human beings while thiamin was still being excreted at a moderately high level. This finding is at variance with the results reported here where normal urinary B.B.S. values were still found with very low thiamin excretion.

The work reported here together with the recent literature on the subject seems to indicate that in adult humans, at least, the level of thiamin excretion, especially after a test dose, is a more sensitive and reliable indicator of the level of thiamin nutrition than are measurements of B.B.S. and pyruvic acid. However, the concentration of thiamin in blood and urine gives no information on the

condition of intermediate carbohydrate metabolism in the body. More research is necessary on the relationships between B.B.S., pyruvic acid and thiamin levels in blood and urine.

Summary. 1. The method for determining bisulfite-binding substances (B.B.S.) is modified and adapted to urine. Interfering substances in urine are removed by adsorption on a preparation of Lloyd's reagent. The pH for the dissociation of the pyruvic acid-bisulfite addition compound has been found to be about pH 6.0.

2. Four normal young adults, 2 men and 2 women, restricted themselves to a diet low in thiamin for varying lengths of time, the maximum being 37 days. No rise in B.B.S. excretion was found during the course of the experiments. Likewise no symptoms were noted, although thiamin excretion was reduced to a very low level.

3. In connection with the results reported here, the recent literature on experimental human thiamin deficiency is briefly reviewed.

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THE RELATIONSHIP BETWEEN THE SPECIFIC GRAVITY AND THE PROTEIN CONTENT IN HUMAN SEROUS EFFUSIONS.

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THE purpose of this investigation was to determine whether a relationship exists between the specific gravity and the protein content of human pathological serous effusions. Although a definite relationship between these two has been established in human

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blood⁴ and in the blood, lymph and edema fluids of dogs,¹⁰ there is considerable disagreement in the literature as to whether there is such a correlation in the transudates and exudates obtained from human serous cavities.^{1,7,8} Reuss, in 1881, evolved a formula expressing this relationship in serous fluids which is partially correct.⁹

Methods. All determinations on fluids were done within 48 hours, since it was found by experiment that even when kept in the icebox the intact protein diminished significantly after that time, although the specific gravity remained about the same. The fluids were centrifuged initially for 10 minutes to remove clots and cells. They were re-centrifuged if further clotting occurred, a not uncommon happening particularly in exudates even after 24 hours. The effect of clotting on the specific gravity and the protein content was found to be insignificant in both exudates and transudates. None of the fluids was markedly hemorrhagic.

The specific gravity was determined by pycnometer and, with 10 exceptions, in duplicate. Ten cubic centimeter pycnometers were fitted with rubber caps to slow the rate of evaporation. This was found to be as efficacious in this regard as the application of vaseline to the capillary stopper as advocated by Moore and Van Slyke.⁴ On each occasion the fluid and distilled water were weighed in the pycnometers at room temperature which during these experiments varied from 21.5° to 29.5°. The weight of the fluid was divided by the weight of the water from the same pycnometer, thus giving the specific gravity at room temperature, $D \frac{t^\circ}{t^\circ}$.

The specific gravity thus obtained was then corrected for temperature by means of the following formulæ:

$$(1) \quad D \frac{20^\circ}{4^\circ} = D \frac{t^\circ}{t^\circ} \times d_{wt}^\circ + (t^\circ - 20^\circ) 0.00026$$

$$(2) \quad D \frac{20^\circ}{20^\circ} = D \frac{20^\circ}{4^\circ} \div d_w 20^\circ$$

(All temperatures are recorded in degrees Centigrade.)

The figures for the density of water at the various room temperatures (d_{wt}°) corrected for expansion and air buoyancy were obtained from Peters and Van Slyke.⁶ The coefficient of expansion of the fluids was found to average 0.00026 by experiment in one transudate and one exudate for the range of temperature at which the experiments were conducted.* Within this range of temperature, the change of $D \frac{t^\circ}{t^\circ}$ (the specific gravity at room

temperature) to $D \frac{20^\circ}{20^\circ}$ (the specific gravity with both fluid and water at 20° C.) added, at most, 0.00029 to the specific gravity. For practical purposes, therefore, no correction need be made for the specific gravity of the fluid as determined at room temperature although such a correction was made in these experiments.

The protein content was determined by the micro-Kjeldahl method, the final nitrogen reading, after Nesslerization, being done by the photoelectric cell colorimeter. The determination of the non-protein nitrogen multiplied by 6.25 was subtracted from the total nitrogen multiplied by 6.25 to give

* Done through the kindness of Dr. S. Howard Armstrong, Jr., Department of Physical Chemistry, Harvard Medical School.

the total protein content. In a few instances the non-protein nitrogen was elevated as high as 155 mg. per 100 cc. This had no significant effect on the results.

Results. The specific gravities and protein contents of 53 fluids were determined consisting of 3 pericardial, 12 peritoneal and 38 pleural fluids.

In Figure 1 are recorded these determinations with the specific gravity expressed as D_{4}^{20} , the more usual definition of specific gravity. In Figure 2 are the same determinations but with the specific gravity expressed as D_{20}^{20} . This is the definition used by

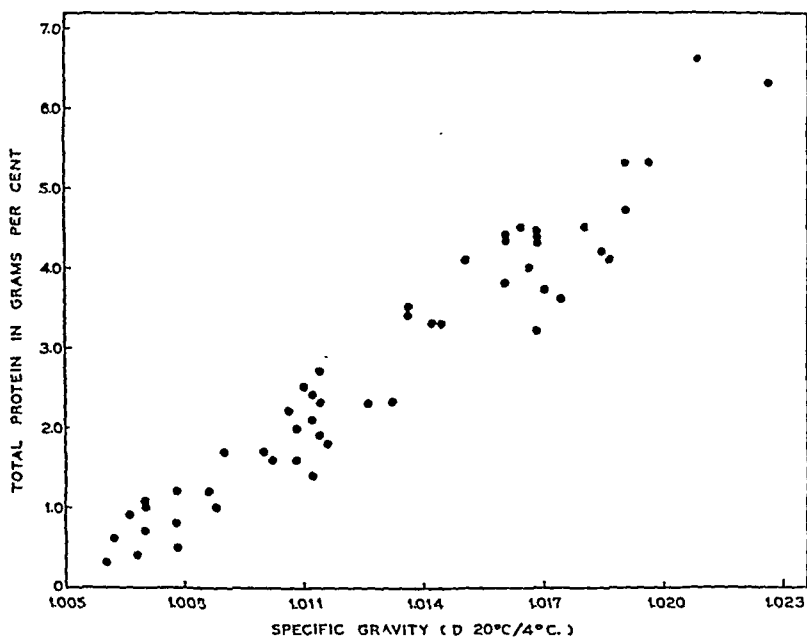


FIG. 1.—The specific gravity, expressed as D_{4}^{20} , and the protein content, expressed in grams per 100 cc., of 52 human serous effusions.

Moore and Van Slyke⁴ and Weech *et al.*¹⁰ in their work on blood, lymph and edema fluid. As shown by comparison of the two charts, this change in definition results in an increase roughly of 0.003 in the specific gravity. In the literature there is usually no agreement on or no recognition of such a change. In the Kagan "falling drop" proteinometer, the specific gravity is expressed as D_{25}^{25} , while in the usual laboratory hydrometer ("urinometer"), it is recorded as $D_{15.5}^{15.5}$.

As shown in Figure 2, there is a good linear correlation between the specific gravity and the protein content of both exudates and transudates. This is expressed by the formula:

$$P = 353 (G - 1.0076)$$

where P = the protein content in grams per 100 cc.

and G = the specific gravity expressed as $D \frac{20^\circ}{20^\circ}$.

This is the same formula derived by Weech *et al.*¹⁰ for transudates from the blood. By this formula the maximum error in the determination of the protein content of effusions from their specific gravity is the same as that of the blood, *i. e.*, 0.6 gm. per 100 cc.⁴

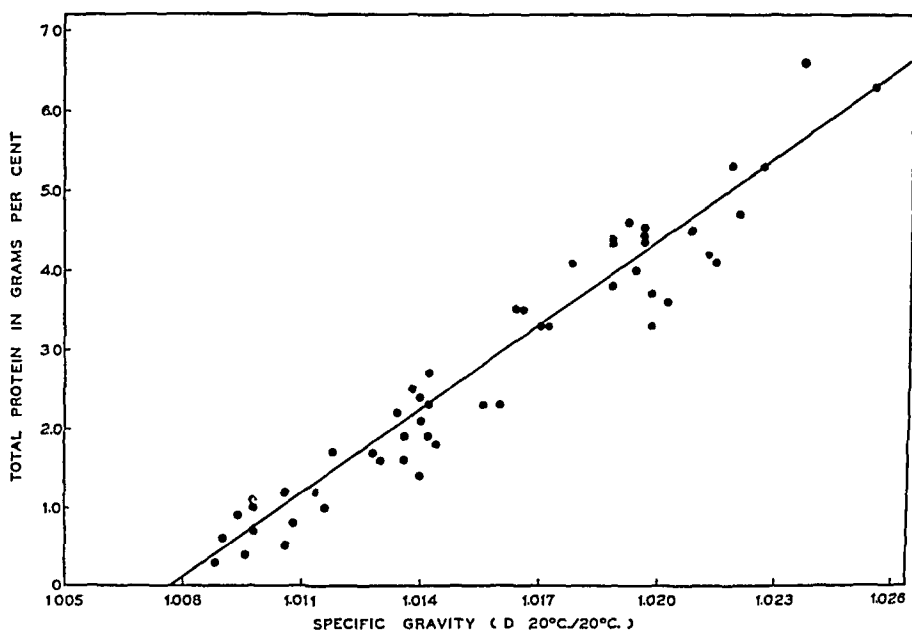


FIG. 2.—The specific gravity, expressed as $D \frac{20^\circ}{20^\circ}$, and the protein content, expressed in grams per 100 cc., of 52 human serous effusions.

In Figure 3 are shown the same determinations as in Figure 2 but with appropriate symbols for the diseases of the patients from whom the fluids were obtained. Although the general rule holds true for the separation of transudates from exudates on the basis of specific gravity (or protein content), there are many exceptions.⁵ There appear to be at least three factors which *may* be responsible for this. The first is the resorption of the fluid with resultant concentration of the unabsorbed protein. This is best illustrated by the occasional cardiac fluid of high specific gravity and protein content in Figure 3. The protein content and specific gravity of cardiac fluids has been shown to increase following diuresis.^{2,3}

Secondly, protein long in a serous cavity may break down with loss of nitrogen into the blood. This theory is advanced as an explanation for a fluid which was the one exception to the specific gravity, protein relationship in our cases. This fluid, which was not charted, was obtained from the pleural cavity of a patient suffering from migratory phlebitis and showed the exceptionally high specific gravity of 1.0522, a protein content of but 5.2 gm. per 100 cc. and a non-protein nitrogen of 39 mg. per 100 cc., all done in duplicate. The cholesterol was 148 mg. per 100 cc. in the fluid. A third factor which may influence, by lowering, the specific gravity (and protein content) of an effusion is a low serum albumin. The cases illustrat-

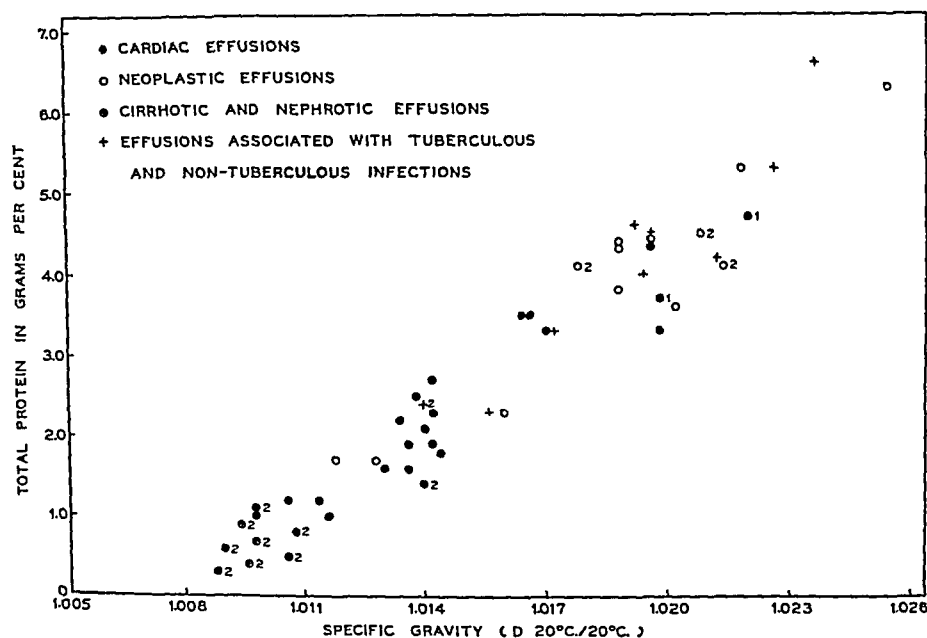


FIG. 3.—The specific gravity, expressed as $D \frac{20^\circ}{20^\circ}$, and the protein content, expressed in grams per 100 cc., with symbols for the associated disease in 52 human serous effusions. 1. Heart disease associated with scleroderma. 2. Serum albumin below 3 gm. per 100 cc.

ing this are noted in Figure 3. This does not appear to play a constant rôle since cases of hypoalbuminemia may have a high protein content in their effusions and *vice versa*.

In a few instances the Kagan "falling drop" proteinometer was used for the determination of the specific gravity of blood serum and of serous fluids of high protein content. In the case of serum, the result thus obtained was less than 0.001 above that obtained by pycnometer, an insignificant difference. In the serous effusions, on the other hand, the specific gravity by the "falling drop" method was as much as 0.0026 above that determined by pycnometer. This presumably is due to differences in physical characteristics.

Summary. Accurate determinations of the specific gravity and protein content was done in 53 serous effusions obtained from the pericardial, peritoneal and pleural cavities of human beings. With one exception there was found to be a linear relationship between the protein content and the specific gravity which was as close as that in the blood. The formula expressing this relationship is the same as that found by Weech *et al.* in the lymph and edema fluid of dogs.¹⁰

The specific gravity and protein content of the various effusions are considered in relation to the diseases of the patients from whom they were obtained. The factors which may influence the specific gravity and protein content are discussed.

The Kagan "falling drop" proteinometer was found to be less accurate for the determination of the specific gravity of serous effusions than of blood serum.

I wish to express my thanks to Dr. Otto Schales, of the Chemical Laboratory of the Peter Bent Brigham Hospital for his help and advice and to the Misses V. Burke and E. Heller for their technical assistance.

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IMMUNE RESPONSE IN DRUG TREATED CASES OF PNEUMOCOCCAL PNEUMONIA.*

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THE host response to the antigenic action of invading pneumococci has long been a subject of study. As early as 1891 the Klemperers⁴ demonstrated that serum taken from pneumonia patients after the crisis displayed curative properties for experimentally infected

* This work was made possible by a grant from the Eli Lilly Company, Indianapolis, Ind.

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rabbits. Further work, by authors too numerous to mention, has revealed the character of the various antibody components and their relation to the course of the disease. It is now known that in patients with pneumonia in whom the disease has not been altered by specific therapy, these protective antibodies may first make their appearance as early as the 3d or 4th day of the disease even though crisis and recovery may not take place for several days. This initial appearance of antibodies is usually in a low titre and they have been found to reach their height about the time of crisis. Following defervescence, the antibody titre may remain high for some time but usually begins to show a decrease in 10 to 14 days.

The theory upon which the serum therapy of pneumonia is based has had its inception and elaboration in these investigations into the immune response to the pneumococcus. Though the clinical features of the disease have been greatly altered by serum therapy, such treatment did not necessitate any change in our understanding of the biology of the pneumococcus or the response of the host. This treatment consists simply of the transfer of artificially induced immune substances from an animal to the human. Little of the recent work concerned with serum therapy has been done in an attempt to correlate it with our previous knowledge, but has been directed largely toward technical improvement in the production and administration of serum.

With the advent of sulfapyridine therapy in pneumococcal infections an entirely different problem is being faced. The exact mode of action of the drug has not been shown, nor do we know much of its effect upon the immune response of the host. There is, of course, the possibility that the drug may actually interfere with the immunologic response of the host to the infection. Edwards, Kircher and Thompson,² however, in a study of 26 cases of pneumococcal pneumonia treated with sulfapyridine, observed no alteration in type-specific and species-specific agglutinin response or the dermal reactivity to the type specific polysaccharide. They also observed no constant relation of the heterophile antibody titre to the clinical course of the pneumonia or to the other antibody responses following sulfapyridine therapy.

This report embraces observations on the presence of agglutinins, mouse-protective power and the polysaccharide skin test in 77 patients treated with type-specific serum and sulfapyridine; 36 patients treated with sulfapyridine and pneumococcus antigen; 14 patients treated with sulfapyridine alone and 2 patients who entered the hospital after the crisis and consequently received no specific therapy. These 129 patients were distributed over Types I, II, III, IV, V, VII, and VIII; 112 of them recovered, 17 died. Observations are also presented on 4 cases of Type XIV pneumonia on which only agglutinin studies and polysaccharide skin tests were done, as the Type XIV pneumococcus is usually avirulent for mice.

Method of Study. Polysaccharide* skin tests were done on each patient before therapy was instituted, about 3 hours after serum therapy, in 24 hours, and at 2- to 5-day intervals thereafter during the hospital stay. Most of the patients were hospitalized for about 2 weeks; a few left earlier, while some were observed over a period of several weeks. Thus, there was considerable variation in the length of time the patients were observed, but all were seen for at least a week after the temperature became normal. Skin testing with the type-specific polysaccharide was done as described by Francis,³ Edwards, Hoagland and Thompson¹ and others, using 0.05 cc. of a dilution of 1:10,000, intracutaneously, with normal saline control. All tests were performed by the same person (L. L. T.), thus eliminating any variation due to individual differences in performance or interpretation. In a small series of patients an attempt was made to demonstrate the passive transfer of skin sensitivity (J. C. E.).

Blood specimens for the determination of agglutinins and mouse protective tests were secured before therapy, the day following therapy and at 2- to 5-day intervals thereafter, a special effort being made to secure one specimen at the time of crisis and one specimen just before death in those patients who died. Blood specimens were submitted to the Eli Lilly Research Laboratories, where agglutinin determinations and mouse protective titres were run. No data were available to those performing these tests except the type of pneumococcus with which the patient was infected. The work was done under the direction of Dr. H. M. Powell.

Agglutinations were done in the usual manner with serum dilutions of 1-5, 1-10 and 1-20. The mouse-protective titre figures represent the number of minimum lethal doses of pneumococci against which 1 cc. of a given serum protected. In arriving at this figure each serum sample was tested at 7 different levels (0-10,000,000). The simple titration figures are used in recording the results and no attempt has been made to reduce them to the standard therapeutic unit.

Pneumococcus vaccine† was given to a group of 10 normal individuals to note any alteration in the polysaccharide skin test and the mouse-protective titre caused by the administration of such antigen.

Method of Treatment. The cases were divided into three series depending upon the therapy received. One series of patients was treated with type-specific rabbit serum and sulfapyridine. This series was subdivided into two groups, depending upon the amount of serum used; (A) On the basis of the suggestion that fractional doses of serum and sulfapyridine if used in combination would be as effective as maximum doses of either agent used alone,^{6a} a selected group of 37 patients, entering the hospital within 96 hours of onset and having but one lobe involved, was given minimum doses (40,000-60,000 units) of type-specific serum and only 0.5 gm. of sulfapyridine at 4-hour intervals. Our clinical results are being published elsewhere.⁸ Suffice it to say here that a large percentage

* Dr. Lewellen Sale, Jr., helped in preparation of the polysaccharide.

† Supplied by Eli Lilly & Co. Each cc. of polyvalent antigen contained:

4	billion pneumococci	Type I
4	"	" II
1	"	" III
2	"	" IV
2	"	" V
1	"	" VII
1	"	" VIII
1	"	" XIV
4	"	DRI

of such patients responded favorably to this therapy. (B) This group comprises all other patients who received the combination of type-specific serum and sulfapyridine. These were patients who, for a variety of reasons, were regarded as sufficiently ill to demand full doses of serum and full doses of drug.

The second series of patients was given sulfapyridine and pneumococcus antigen. The use of pneumococcus antigen was stimulated by recent experimental studies^{5,6b} suggesting that sulfapyridine would be more efficient in a patient also receiving pneumococcus antigen. Each patient received 1 cc. of polyvalent antigen (pneumococcus vaccine as mentioned above) every 6 to 12 hours. A total of 8 cc. was given during the first 4 days of hospitalization. Sulfapyridine was given in maximum dosage of 1 gm. per hour for 4 doses, followed by 1 gm. every 4 hours until the temperature had remained normal for 2 days, when the dose was cut in half.

The third series of patients was given sulfapyridine alone. Here also the maximum dosage scheme was utilized.

In all patients receiving the larger dosage of sulfapyridine, the oral administration was supplemented by the sodium salt given intravenously when necessary. Indications for such supplementary therapy were inability of the patient to retain the drug by mouth, or lack of response to therapy in the face of insufficient blood concentrations. Five to 10 mg. per 100 cc. were considered adequate levels with an optimum of 7.5 to 8 mg. per 100 cc. However, there was good clinical response in many cases with levels below 5 mg. per 100 cc. so no attempt was made to attain a higher level. Thus, there was some variation in the total amount of sulfapyridine received by the individual patients. The drug was discontinued after 4 days of normal temperature.

Results and Discussion. *Polysaccharide Skin Test.* It is expected on the basis of previous studies that a large percentage (95%) of patients recovering spontaneously from a pneumococcal pneumonia should give a positive dermal reaction with type-specific capsular carbohydrate.¹ The titre of type-specific antibody must be considerable before the skin test is positive, and where no antibodies have been added (*i. e.*, no serum given) the skin tests may remain negative even where there are sufficient antibodies present for recovery. It is also recognized that the test may become positive in cases which may later prove fatal due to extrapulmonary foci of infection such as meningitis, empyema and endocarditis.

Analysis of the series of patients receiving combined serum-sulfapyridine therapy reveals that in Group A (Table 1), where the smaller doses of serum were used, 16 of 37 (45%) of the patients showed a positive reaction. In Group B, where the maximum doses of serum were used, 18 of 32 cases (56%) showed a positive test at some time during the period of observation. Thus, of a total of 69 patients, 34 (49%) showed a positive dermal reaction (Table 2).

TABLE 1.—SUMMARY OF ALL RECOVERED CASES.

Therapy.*	No of cases.	Pos. SSS skin tests.	Agglutinins.			Mouse protective titres.		
			1-5.	1-10.	1-20.	Less than 1000.	1000 to 1,000,000.	1,000,000 or more.
Type I:								
100,000 units or more serum	15	5	3	1	4	0	0	13
Less than 100,000 units serum	14	6	0	1	0	0	1	13
Antigen	2	1	0	0	1	0	0	2
Sulfapyridine alone	5	1	0	0	0	0	3	2
Type II:								
None	1	1	0	0	1	0	0	1
100,000 units or more serum	5	2	0	0	5	0	0	5
Less than 100,000 units serum	5	4	0	1	4	0	0	5
Antigen	1	0	0	0	1	1	0	0
Sulfapyridine alone	3	0	0	0	1	0	2	1
Type III:								
100,000 units serum	2	2	0	1	1	0	2	0
Antigen	20	4	2	3	1	11	4	5
Sulfapyridine alone	1	0	0	0	0	0	1	0
Type IV:								
None	1	1	0	0	0	0	1	0
Antigen	5	3	0	1	1	0	1	4
Sulfapyridine alone	1	0	1	0	0	0	1	0
Type V:								
100,000 units serum or more	2	1	0	0	1	0	0	2
Less than 100,000 units serum	3	0	0	0	3	0	0	3
Antigen	1	0	0	0	0	0	1	0
Sulfapyridine alone	2	0	1	0	0	0	2	0
Type VII:								
100,000 units serum or more	6	5	0	1	5	0	0	6
Less than 100,000 units serum	1	0	0	0	1	0	0	1
Antigen	2	2	0	0	2	0	1	1
Sulfapyridine alone	1	1	0	0	0	0	0	1
Type VIII:								
100,000 units or more serum	2	1	0	0	2	0	0	2
Less than 100,000 units serum	12	5	0	5	5	0	6	6
Antigen	1	0	0	0	1	0	0	1
Type XIV:								
100,000 units or more serum	2	2	0	0	2			
Less than 100,000 units serum	2	1	1	0	1			

TABLE 2.—SUMMARY OF RECOVERED CASES TREATED WITH SULFAPYRIDINE AND SERUM.

Type.	No. of cases.	Pos. SSS skin tests.	Agglutinins.			Mouse protective titre.		
			1-5.	1-10.	1-20+.	Less than 1000.	1000 to 1,000,000.	1,000,000 or more.
I	27	11	3	2	4	0	1	26
II	10	6	0	1	9	0	0	10
III	2	2	0	1	1	0	2	0
V	5	1	0	0	4	0	0	5
VII	7	5	0	1	6	0	0	7
VIII	14	6	0	5	7	0	6	8
XIV	4	3	1	0	3			
Total	69	34	4	10	34	0	9	56

* All cases also received sulfapyridine.

Tables 1 and 3 also show the results of the skin tests of those patients treated with sulfapyridine and antigen. Ten of 32 patients (31%) showed a positive polysaccharide test. Of the series of patients receiving sulfapyridine alone (Tables 1 and 4), of 12 patients, 2 (15%) showed positive reactions. In further study of

TABLE 3.—SUMMARY OF RECOVERED CASES TREATED WITH SULFAPYRIDINE AND ANTIGEN.

Type.	No. of cases.	Pos. SSS skin tests.	Agglutinins.			Mouse protective titre.		
			1-5.	1-10.	1-20+.	Less than 1000.	1000 to 1,000,000.	1,000,000 or more.
I	2	1	0	0	1	0	0	2
II	1	0	0	0	1	1	0	0
III	20	4	2	3	1	11	4	5
IV	5	3	0	1	1	0	1	4
V	1	0	0	0	0	0	1	0
VII	2	2	0	0	2	0	1	1
VIII	1	0	0	0	1	0	0	1
Total	32	10	2	4	7	12	7	13

TABLE 4.—SUMMARY OF RECOVERED CASES TREATED WITH SULFAPYRIDINE ALONE

Type.	No. of cases.	Pos. SSS skin tests.	Agglutinins.			Mouse protective titre.		
			1-5.	1-10.	1-20+.	Less than 1000.	1000 to 1,000,000.	1,000,000 or more.
I	5	1	0	0	0	0	3	2
II	3	0	0	0	1	0	2	1
III	1	0	0	0	0	0	1	0
IV	1	0	1	0	0	0	1	0
V	2	0	1	0	0	0	2	0
VII	1	1	0	0	0	0	0	1
Total	13	2	2	0	1	0	9	4

TABLE 5.—SUMMARY OF ALL DEATHS.

	No. of cases.	Pos. SSS skin tests.	Agglutinins.			Mouse protective titres.		
			1-5.	1-10.	1-20+.	Less than 1000.	1000 to 1,000,000.	1,000,000 or more.
Sulfapyridine and serum:								
Type I	3	0	0	0	0	2	1	0
II	3	0	0	0	3	0	0	3
V	3	1	0	0	2	1	0	2
VII	1	1	0	0	1	0	1	0
VIII	2	0	0	0	2	0	0	2
Sulfapyridine and antigen:								
Type III	4	0	1	0	0	2	2	0
Sulfapyridine alone:								
Type IV	1	0	0	1	0	0	1	0
Total	17	2	1	1	8	5	5	7

Tables 2 and 3 the striking failure of Type III cases to develop positive skin tests is noted. If these Type III cases are excluded from these two series, there remain 12 cases treated with sulfapyridine and antigen, giving 6 (50%) positive reactions and 12 cases treated with sulfapyridine alone giving 2 (16%) positive reactions.

The low percentage of positive dermal reactions in these cases recovering from pneumonia is surprising. In cases where the skin test remains negative in spite of good response to adequate amounts of serum, it may be well to use higher dilutions of the type-specific polysaccharide than 1-10,000.

There were positive polysaccharide tests in 2 patients who subsequently died. None of the other 15 who died ever showed a positive reaction. One of the positive reactions occurred in a Type V case where the reaction became positive immediately after the administration of serum. The test subsequently became negative and remained so despite a high agglutinin titre and mouse protective titre. Death occurred 9 weeks after admission and autopsy revealed a vegetative endocarditis and meningitis. The other positive test occurred in a patient with a pneumonia of Type VII. The test became positive after administration of 200,000 units of serum, at which time the temperature dropped to normal. The patient seemed to be recovering nicely but on the 10th day developed serum sickness and one day later a thyroid crisis occurred in spite of the previous administration of iodine in large quantities. The patient died with a terminal temperature of 41.5°. The polysaccharide skin test was positive only 2 hours before death.

Two patients showed positive skin tests on admission to the hospital. One (Type IV) had had a crisis and was clinically well, therefore, raising no question as to therapy. The other case, a Type II infection, was admitted the 8th day of the disease and was still critically ill with a temperature of 39.5° C. On the basis of the positive reaction specific therapy was withheld, and in 12 hours clinical crisis occurred and an uneventful recovery ensued. It is probable that in the latter case, had the skin test not been done, large doses of both serum and sulfapyridine would have been given unnecessarily.

Thus it seems that the presence of a positive polysaccharide skin test may be expected in about one-half of the patients receiving less than optimum amounts of serum combined with sulfapyridine. A higher percentage of positive reactions is seen in individuals receiving more nearly maximum amounts of serum with sulfapyridine. An even smaller percentage of positive reactions is seen in cases treated with sulfapyridine and antigen. The antigen, in the small number of patients studied, appeared to increase the number of positive reactions over those occurring when sulfapyridine alone was given. A negative skin test in a patient treated with sulfapyridine does not forecast death; but, on the other hand, a positive reaction is far more significant and is of value prognostically and as a guide for limitation of further therapy.

The blood serum of 5 patients, who gave positive type-specific polysaccharide skin tests after serum therapy, was injected intra-

cutaneously (0.2 cc.) in 24 healthy persons with negatively reactive skins. Twenty-four hours later 0.03 cc. of 1:10,000 solution of type-specific polysaccharide was injected in the same area. Negative results were obtained. Several positive results were obtained when the polysaccharide was injected within 2 or 3 hours after the injection of serum. This suggests the absence of a reagin or a true Prausnitz-Küstner reaction.⁷

Agglutinins. The various tables show the results of our study of agglutinin titres in the patients observed. In none of the cases were agglutinins present on admission. The titre was frequently at its height in the first specimen drawn after the administration of serum. However, in some instances the titre continued to rise for several days thereafter. An analysis of the tables shows that of the 69 cases receiving sulfapyridine and serum, 48 (69%) showed agglutinins of some titre at some time during the period of observation. The lowest agglutinin response was seen in Type I infections where only 9 of 27 (33%) showed an appreciable titre. All of the other types given serum showed the appearance of agglutinins in a high percentage of cases.

Of the 32 cases receiving sulfapyridine and antigen therapy, 13 (40%) showed agglutinins in a titre of 1-5 or more. If, however, the Type III cases are excluded there remain 12 cases, 7 of whom (58%) showed agglutinins. Of the 20 cases of Type III infection only 6 (30%) showed agglutinins and only 1 of these reached a titre of 1-20.

Of the 13 cases of pneumococcic pneumonia treated with sulfapyridine alone, only 3 (21%) showed an appreciable titre. There was only 1 Type III case in this group and it showed no response.

Of the 2 patients who recovered without therapy, 1 (Type II) showed a satisfactory response, while the other (Type IV) showed no agglutinins at dilutions of 1-5 or above, despite a positive skin test and satisfactory mouse-protective power.

The agglutinin response was also studied in 17 patients who died. Nine of these cases showed agglutinins in a titre of 1-5 or more, 7 of them rising to 1-20 or above. All 7 cases with the high titre, however, were confined to the group receiving 100,000 or more units of serum. It is interesting to note that in 6 of these cases upon whom blood specimens were collected within a few hours of death, only 1 showed a decrease or disappearance of the agglutinins. The other 5 maintained a titre of 1-20 or above until death. There was 1 death in the group treated with sulfapyridine alone. This case was due to Type IV pneumococcus and during the period of observation showed an increasing mouse-protective titre (0-10,000), and agglutinins appeared in 1-10 dilution, but the polysaccharide skin test remained negative. There were 4 deaths in Type III infections, all of whom received sulfapyridine and antigen. Two of these

cases never manifested any antibody response, either polysaccharide skin test, agglutinins or mouse-protective power. The other 2 showed an appreciable mouse-protective titre (10,000 or above), but only 1 showed agglutinins in 1-5 dilution.

In conclusion, one might say from our experience that agglutinins appear more promptly and in highest percentage in those cases treated with serum and sulfapyridine. The series of patients treated with sulfapyridine and antigen developed agglutinins to a less degree than those treated with sulfapyridine and serum, but definitely to a greater degree than those treated with sulfapyridine alone. It seems that the presence of agglutinins in a titre of 1-5 or higher, or even in increasing titre, is no assurance of recovery and that a positive polysaccharide skin test is a more accurate prognostic sign.

Mouse-Protective Power. The combined phenomena of agglutination, precipitation, and opsonization are complement forces which contribute to the total protective power of the animal against invading pneumococci. That there is a close correlation between the protective power and the various antibodies has been well shown. Sulfapyridine, however, is an additional factor which must be considered in evaluating the protective power of the sera from the patients in this series. All of the patients received sulfapyridine and even the small amounts present in the serum may have enhanced its protective power for mice. That this factor played a large part, however, seems unlikely as many of the samples taken while the blood sulfapyridine levels were at their height, failed to show any protective properties. It is recognized that the agglutinin observations and the mouse-protective power as run are not comparable quantitatively. The mouse-protective test is a more delicate index of antibody response. Thus, there may be evidence of mouse protection without demonstrable agglutinins. On the other hand, in the presence of agglutinins a rather high mouse-protective power is expected.

Though the sera were tested at seven different levels, for purposes of analysis and discussion the titres have been divided into three classes. The lowest class includes all of those below 1000 M.L.D., the second includes those of 1000 to less than 1,000,000, while into the third are those of 1,000,000 or more.

Of the cases treated with sulfapyridine and serum almost every one that recovered showed a high mouse-protection titre. In fact, of the 30 patients receiving 100,000 or more units of serum, only 2 failed to show a titre of 1,000,000 or more; both of these cases were Type III infections. Only 7 of 35 cases receiving less than 100,000 units of serum failed to show a titre of 1,000,000 or more, and 6 of the 7 were Type VIII cases. In none of the recovered patients receiving serum did the titre remain below 1000, and in 86% of the cases it was 1,000,000 or more at some stage of the disease.

Comparable mouse-protective power cannot be shown for the two series receiving sulfapyridine and antigen or sulfapyridine alone. Only 13 of the 32 cases (40%) who recovered with sulfapyridine and antigen showed a titre of 1,000,000 or more, while 12 (37%) had titres of less than 1000. It seems significant, however, to state that of these showing comparatively little response, 11 were Type III infections. Stated differently, 11 of 20 cases (55%) of Type III pneumonia who recovered under sulfapyridine-antigen therapy failed to show any appreciable mouse-protective power in the serum. If the Type III cases are excluded from this series, 9 of 12 (75%) showed titres of 1,000,000 or more, and only 1 of the 12 (8.3%) failed to show any appreciable protective power. These figures then compare favorably with those seen above in the serum-sulfapyridine treated group.

Thirteen patients who received sulfapyridine alone recovered. Analysis of the results of mouse-protection tests in these cases shows that 4 (30%) developed a titre of 1,000,000 or more, while the remaining 9 cases showed a titre of above 1000. Inasmuch as there was only one Type III pneumonia in this group, little change would be wrought in these figures by excluding this case.

The mouse-protective titre in the 2 cases recovering without therapy reveals that the titre in one Type IV case was only 10,000. This was the case that did not show agglutinins. One Type II patient had a titre of 10,000,000 on admission.

Analysis of the mouse-protective power in the 17 deaths reveals that most of the patients treated with serum and sulfapyridine (7 of 12) showed a titre of 1,000,000 or more, but that 3 showed a titre of less than 1000. On the other hand, none of the 5 patients who died who were given sulfapyridine and antigen or sulfapyridine alone showed a titre as high as 1,000,000 and 2 of them failed to show a titre as high as 1000.

Summarizing the mouse-protection studies, one may say that most of the patients recovering from pneumococcal pneumonia, except for Type III infections, show a high titre regardless of treatment. Less than half of the Type III cases showed any appreciable mouse-protective power. The largest percentage of high titres is seen in the serum-sulfapyridine treated group, of which Type VIII was strikingly lowest. Further, if Type III cases are excluded, the sulfapyridine-antigen treated cases showed a better response than those treated with sulfapyridine alone. Analysis of the deaths, however, indicates that the mouse-protective power is not a good prognostic sign, as a large percentage of the patients who die have a high protective titre.

The normal individuals who were given the polyvalent pneumococcus vaccine showed very little response in so far as the polysaccharide skin test was concerned. In all of the individuals, before

the vaccine was given, the test with the use of Type I and Type II specific polysaccharide was negative. In one individual the test against Type I became positive on the 8th day and remained so through the 15th day. Skin tests for Type II remained negative throughout. In a second individual the test with the Type I polysaccharide became positive on the 15th day but test with Type II remained negative. Thus 2 patients out of 10 developed a positive skin test against the specific polysaccharide of Type I only. None of the 10 developed a positive reaction with Type II.

The mouse protection titre of these normal individuals gave more suggestion of immune response to the vaccine. Before the administration of vaccine, 2 of the individuals showed a mouse protection titre of 10 M.L.D. In these 2 individuals, by the 15th day, the titre had risen to 10,000,000 or more M.L.D. Six of the remaining 8 who showed no protection before the administration of the vaccine developed titres of 10,000,000 M.L.D. or better within a 2-weeks' period. One individual developed a titre of only 1,000,000 M.L.D. and 1 had a titre on the 15th day of only 10,000 M.L.D.

Conclusions. 1. The type-specific polysaccharide skin test is a more reliable aid in the prognosis of pneumococcic pneumonia than the mouse-protective titre or the agglutinin concentration of the patient's serum, especially in those patients receiving adequate amounts of serum.

2. A limited number of observations indicated that the type-specific polysaccharide skin test is not passively transferred.

3. The combination of pneumococcus antigen with sulfapyridine resulted in a higher percentage of positive type-specific polysaccharide skin tests, in more positive agglutinin tests and in a higher mouse-protective power than were observed in the limited number of cases (12) when sulfapyridine was used alone.

4. Patients with Type III pneumonia are in a class distinct from others. The immune response as gauged by the tests in this study are not stimulated to the same degree as in other types of pneumococci.

5. Death occurs in certain cases in spite of apparently adequate antibody response, so far as can be determined by the observations as indicated above.

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SULFADIAZINE AND SULFATHIAZOLE IN THE TREATMENT
OF PNEUMOCOCCIC PNEUMONIA.

A PROGRESS REPORT ON 200 CASES.*

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ADVANCES in the chemical treatment of pneumonia have been occurring during the past 3 years at an ever-accelerating pace. To consolidate these advances and to evaluate the comparative merits of various chemotherapeutic agents it will be necessary to accumulate extensive data from different sources over a period of years. Of considerable interest would be data collected in a single hospital where the different compounds are being used. In previous papers^{2,3,5,9} we have reported our clinical experiences with the use of sulfapyridine and sulfathiazole. At this time we wish to present our observations on the comparative therapeutic effectiveness and toxicity of sulfadiazine and sulfathiazole in the treatment of pneumonia.

Sulfadiazine,‡ 2-sulfanilamido pyrimidine, synthesized by Roblin *et al.*,⁸ is the pyrimidine analogue of sulfapyridine. Its therapeutic effectiveness and toxicity in experimental animals has been investigated by Feinstone *et al.*,¹ who found that the drug had a high therapeutic activity against pneumococcal infection and caused less tissue damage than either sulfapyridine or sulfathiazole. The behavior of sulfadiazine in man has been reported by Plummer and Ensworth⁶ and by us.⁷ It was found that the drug is readily absorbed from the gastro-intestinal tract, is not excreted as readily as sulfathiazole, and disappears from the blood slowly. Sulfadiazine is readily secreted into peritoneal and pleural fluids with resultant concentrations approximating those in the blood. In cerebrospinal fluid, concentrations averaging 50% of the blood value were found.

* Aided by a grant from the American Philosophical Society.

† Detailed for this and related studies on pneumonia by the Pennsylvania Department of Health, Division of Pneumonia Control.

‡ The sulfadiazine used in this study was supplied us by Dr. Howard Hogan, Nepera Chemical Company, Yonkers, N. Y.

Organization of the Study. A primary requirement in the evaluation of a new chemotherapeutic agent for pneumonia is to compare it with a proven form of therapy. Therefore, from the beginning of this study (November, 1940) the medical services* in the hospital were divided into two therapeutic groups, so that approximately half of the pneumonia patients received the new drug, sulfadiazine, while the other half served as controls and were given sulfathiazole. For this report we have taken the first 173 typed cases (87 sulfadiazine, 86 sulfathiazole) and, in addition, the first 13 non-typed sulfadiazine treated patients and the first 14 non-typed sulfathiazole treated patients.

The diagnosis of pneumonia was established by the clinical history and the findings on physical examination. When indicated, the diagnosis was confirmed by Roentgen studies. A specific pneumococcus type was recovered from the sputum or blood stream in 173 patients and in 27 the sputum failed to yield a type with pneumococcus serum Types I to XXXIII. Repeated blood counts and urinalyses, as well as blood cultures, were made in all patients. Determinations of free and total drug in the blood were made on all patients receiving either sulfadiazine or sulfathiazole. Special studies were performed on most of the daily urine samples for crystals of both drugs. Other laboratory procedures were carried out as indicated.

Dosage. The following dosage was employed: With sulfadiazine, an initial 3 gm. dose by mouth was followed by 1 gm. every 4 hours, unless signs of severe toxicity developed. Treatment was continued until the temperature remained normal for 48 hours, along with evidence of clinical improvement. With sulfathiazole, the dose schedule was the same as that used with the new drug, except that the first 3 gm. dose was repeated in 4 hours. This added quantity of sulfathiazole was used because previous experience has shown this to be an effective dosage.⁵ In general, the total dosage was 25 to 35 gm., depending on the physical and laboratory findings in each case. The average total dosage for patients receiving sulfadiazine was 27 gm., as compared to 29.9 gm. for the sulfathiazole treated group. Type specific serum was administered when necessary. The indications for combined therapy cannot be specifically stated as each patient must be handled as an individual problem. In every instance that serum was used we were of the opinion that drug treatment alone was inadequate. It is our clinical judgment that additional therapy with specific serum is indicated in selected cases. Of the 200 patients included in this report, 18 (11 sulfadiazine, 7 sulfathiazole) received specific serum along with chemotherapy.

* Clinical facilities were given us for this study by the following Chiefs of Service: Doctors, R. S. Boles, C. L. Brown, H. D. Jump, Thomas Klein, D. W. Kramer, S. A. Loewenberg, W. E. Robertson, H. W. Schaffer, T. G. Schnabel, and the late R. G. Torrey.

In certain instances, where a rapid elevation of the blood level of either drug was desired, a 5% solution of the sodium salt of either drug (0.06 gm. per kilo of body weight) was administered intravenously as a supplement to oral therapy. The administration of 3 gm. of sulfadiazine sodium intravenously gave free blood levels of approximately 11.9 mg. per 100 cc. within 15 minutes. Furthermore, concentrations above 6 mg. per 100 cc. were readily maintained for at least 8 hours. Because of the slow excretion rate of sulfadiazine, the parenteral treatment of pneumonia appears to present practical possibilities. Further studies on this aspect of pneumonia therapy are in progress.

Therapeutic Results. In this report we have included all patients with a diagnosis of pneumonia who received drug therapy, except those with empyema or meningitis on admission. The results of treatment in the two therapeutic groups are shown in Table 1. Of

TABLE 1.—DISTRIBUTION OF TYPES, BACTERIEMIA, AND MORTALITY RATES.

Type.	Sulfadiazine treated.				Sulfathiazole treated.			
	All cases.		Bacteriemic cases.		All cases.		Bacteriemic cases.	
	No.	Died.	No.	Died.	No.	Died.	No.	Died.
I	15	1	7	1	14	..	3	..
II	3	2	..	1	..
III	15	4	3	2	18	7	3	3
Others	54	6	7	4	52	9	7	5
Non-typed	13	14	1
Total	100	11	17	7	100	17	14	8
Mortality, %	11.0		41.2		17.0		57.1	
Corrected mortality, %*	6.3		23.1		11.5		33.3	

the patients treated with sulfadiazine, 11 died (Table 2). In the sulfathiazole treated group there were 17 deaths (Table 2). Patients who were moribund on admission and died within 24 hours were included, although they did not provide a fair trial for either drug. Five such patients were treated with sulfadiazine and 8 with sulfathiazole. If these cases are excluded, the corrected mortality becomes 6.3% and 11.5% respectively for the sulfadiazine and sulfathiazole treated groups. Seventeen patients with bacteriemia were treated with sulfadiazine and 7 of these died (41.2% mortality). If the 4 bacteriemia patients, dying within 24 hours, are excluded, the corrected mortality in this sub-group is 23.1%. In the sulfathiazole treated group, 8 of the 14 bacteriemia patients died, and if the 5 24-hour cases are excluded, the corrected mortality becomes 33.3%.

In general, the distribution of race, sex (Table 3), age (Table 4), and day of disease on which treatment was begun (Table 5) were comparable in the two therapeutic groups. Although the number

* Does not include 13 patients (5 sulfadiazine, 8 sulfathiazole) who died in less than 24 hours after admission; 9 of these cases had bacteriemia (4 sulfadiazine, 5 sulfathiazole).

of cases is small, it is a striking fact that no sulfadiazine treated patients died when therapy was administered within the first 3 days of illness (Table 5).

TABLE 2.—ANALYSIS OF FATAL CASES.

No.	Age, yrs.	Day of disease treatment begun.	Type.	Blood culture.	No. of Lobes involved.	Total drug, gm.	Total serum, units.	Remarks.
SULFADIAZINE.								
1*	59	14	I	Pos.	1	6	..	Moribund on adm., died in 12 hrs. Aut.: Lobar pneum., ac. supp. pericarditis.
2	60	7	III	Neg.	1	11	..	Asthma, card. decomp. No autopsy.
3	52	4	III	Pos.	3	40	100,000	Poor response to therapy. Sudden abd. catastrophe. Aut.: Perf. duod. ulcer, diffuse peritonitis, pul. abscess, resolving br.pneum.
4	72	8	III	Neg.	3	42	..	Responded well to therapy. Ready for discharge, sudden card. decomp. No aut.
5*	66	4	III	Pos.	1	7	..	Moribund on adm., died in 20 hrs. Asthma. No aut.
6	53	10	IV	Pos.	1	27	200,000	Toxic hepatitis (Ict. index 50 u.), card. decomp. on adm. No aut.
7*	60	8	IV	Pos.	2	7	..	Moribund on adm., died in 18 hrs. No aut.
8*	65	9	VI	Neg.	2	4	..	Chr. alcoholism, sudden death 22 hrs. after adm. Aut.: lob. pneum., degen. of liver, hypert. and dil. of heart.
9	76	4	XI	Pos.	2	28	..	Responded to therapy. Card. decomp. Azotemia (B.U.N. 65). No aut.
10*	38	4	XIV	Pos.	2	7	..	Moribund on adm., died in 20 hrs. Aut.: Lobar pneum.
11	47	5	XXIII	Neg.	2	41	100,000	No response to therapy. No autopsy.
SULFATHIAZOLE.								
1	75	5	III	Neg.	3	47	100,000	Card. decomp. No autopsy.
2*	48	9	III	Pos.	3	7	..	Moribund on adm., died in 14 hrs. Aut.: Lobar pneum.
3*	60	7	III	Neg.	3	7	100,000	Moribund on adm., died in 12 hrs. Aut.: Lob. pneum.
4*	67	5	III	Neg.	1	6	..	Pulm. tuberculosis, died 6 hrs. after adm. No aut.
5	67	10	III	Neg.	2	21	..	Cardiac failure, azotemia on adm. (B.U.N. 44). No aut.
6	59	5	III	Pos.	3	12	30,000	Serum sensitive. Over 1000 colonies per cc. blood. Aut.: Lob. pneum.
7*	39	4	III	Pos.	1	6	100,000	Moribund on adm., died in 10 hrs. Rheumatic ht. dis. Hypert., bl. pr.: 200/120. Azotemia (B.U.N. 85). Aut.: Lob. pneum., card. hypert., mitr. and aor. lesions.
8*	60	7	IV	Pos.	1	6	..	Moribund on adm., died in 12 hrs. Chr. alcoholism. Aut.: Lob. pneum.
9*	19	5	IV	Pos.	5	8	..	Moribund on adm., with leukopenia (2000 lts.). Died in 12 hrs. Aut.: Lob. pneum.
10	74	9	IV	Pos.	2	22	..	Lutetic ht. dis. with failure. Azotemia (B.U.N. 70) on adm. No aut.
11	52	4	VI	Neg.	2	10	..	Severe diabetes mellitus, ac. cor. occlusion, died in 36 hrs. No autopsy.
12*	27	3	VII	Neg.	1	7	..	Delirium tremens. Died in 14 hrs. after adm. Aut.: Lob. pneum.
13	40	5	IX	Neg.	4	8	..	Moribund on adm., died in 30 hrs. Aut.: Lob. pneum.
14	60	11	XVII	Neg.	2	8	..	Severe asthma, died in 32 hrs. No aut.
15*	44	7	XVII	Pos.	3	3	..	Moribund on adm., died in 8 hrs. Aut.: Lob. pneum.
16	59	3	XVIII	Pos.	3	20	100,000	Azotemia (B.U.N. 145), leukopenia (4000 lts.) on adm. No autopsy.
17	65	1	1	27	..	Responded well to treatment. Cerebral thrombosis 23 days before adm. Aut.: bronchopneum., thrombosis of cerebral and cor. arteries.

* Patient died within 24 hours after admission.

TABLE 3.—MORTALITY ACCORDING TO RACE AND SEX.

Race.	Sex.	Sulfadiazine treated.		Sulfathiazole treated.	
		No.	Died.	No.	Died.
White	Male	39	8	28	7
	Female	11	1	18	2
Negro	Male	38	2	33	7
	Female	12	..	21	1

TABLE 4.—MORTALITY ACCORDING TO AGE GROUPS.

Age group, years.	Sulfadiazine treated.		Sulfathiazole treated.	
	No.	Died.	No.	Died.
12-19	8	..	4	1
20-29	17	..	17	1
30-39	25	1	20	1
40-49	17	1	23	3
50-59	12	3	22	3
60-69	16	4	9	6
70 and over	5	2	5	2

TABLE 5.—MORTALITY IN RELATION TO DAY OF DISEASE ON WHICH TREATMENT WAS BEGUN.

Day of disease treatment started.	Sulfadiazine treated.		Sulfathiazole treated.	
	No.	Died.	No.	Died.
1	9	..	8	1
2	14	..	19	..
3	24	..	18	2
4	14	4	11	2
5	14	1	14	5
6	8	..	8	..
7	8	1	13	3
7+	9	5	9	4

Influence of Treatment on the Course of the Disease. In evaluating any therapeutic agent, one must consider the effect of the agent on the course of the disease, as well as its influence on the mortality incidence. As shown in Table 6, a critical drop in temperature occurred within 24 hours in 66.3% of the patients treated with sulfadiazine as compared to 60.2% of the patients in the sulfathiazole treated group. At the end of 48 hours 87.6% of the patients in the sulfathiazole treated group. At the end of 48 hours, 87.6% of the patients receiving sulfadiazine showed a critical drop in temperature compared with 74.7% of the patients treated with sulfathiazole. The temperature fell to normal within 24 hours in 23.6% of the patients in the sulfadiazine treated group and in 15.7% of the patients receiving sulfathiazole. Within 48 hours normal temperature occurred in 61.8% and 44.6% of patients in the sulfadiazine and sulfathiazole groups, respectively. A secondary rise in temperature occurred in 10 patients (6 sulfadiazine, 4 sulfathiazole) and these usually required further drug therapy. Cases in which a diagnosis of drug fever was made are not included in this group. The average number of hospital days for patients in each therapeutic group is practically the same (13.6 days sulfadiazine, 13.3 days sulfathiazole). Not included in the latter group are all deaths and patients who remained in the hospital for various associated conditions (empyema, paresis, diabetes mellitus, heart disease, and so on).

TABLE 6.—EFFECT OF TREATMENT ON TEMPERATURE AND HOSPITAL STAY.

	Sulfadiazine treated.		Sulfathiazole treated.	
	No.	%.	No.	%.
Critical fall in temperature:*				
Within 24 hours	59	66.3	50	60.2
Within 48 hours	19	21.3	12	14.5
Within 72 hours	8	9.6
Over 72 hours	11	12.4	13	15.7
Temperature at normal level:*				
Within 24 hours	21	23.6	13	15.7
Within 48 hours	34	38.2	24	28.9
Within 72 hours	13	14.6	14	16.9
Over 72 hours	21	23.6	32	38.5
Secondary rise in temperature (above 99° F.)*	6		4	
Average stay in hospital	13.6 days		13.3 days	

* All deaths excluded.

Not included in this group are all deaths and patients kept in hospital for further study and treatment of accompanying conditions.

Complications. The incidence of complications was low and little different in the two therapeutic groups. Empyema developed in 2 cases, 1 with each drug; both patients recovered. Massive pleural effusion occurred in 5 cases (3 sulfadiazine, 2 sulfathiazole) with no deaths. The diagnosis of lung abscess was made in 2 patients receiving sulfadiazine, with 1 death.

Toxic Reactions. In this series of 200 patients the incidence and severity of toxic reactions was comparable for the two therapeutic groups. Nausea and vomiting was mild and infrequent in both groups. In only 1 instance was it necessary to stop drug therapy because of severe vomiting and this occurred in a sulfadiazine treated patient who also developed a skin rash.

TABLE 7.—INCIDENCE OF TOXIC REACTIONS (200 CASES).

Toxic reactions.	Sulfadiazine treated (incidence, %).	Sulfathiazole treated (incidence, %).
Nausea	10.0	21.0
Vomiting:*		
Mild	4.0	8.0
Moderate	1.0
Severe	1.0	..
Total	5.0	9.0
Hematuria—microscopic	4.0	9.0
Dermatitis	1.0	2.0
Conjunctivitis	1.0
Psychosis?	7.0	3.0
Drug fever?	1.0	2.0
Leukopenia (below 5000 W.B.C.)	2.0	2.0
Neutropenia (below 40% P.M.N.)	1.0

* Mild—less than three times; moderate—three or more times; severe—necessitated stopping the drug.

Microscopic hematuria was encountered in 4 patients receiving sulfadiazine and in 9 patients treated with sulfathiazole. Gross hematuria was not observed with either drug. In most instances daily examination of urine sediment was made especially for evidence of drug crystals. Approximately 29% of the sulfadiazine treated patients had urinary crystals as compared to 70% of those receiving sulfathiazole. Furthermore, sulfadiazine treated patients usually

had a smaller number of crystals in the individual specimens examined. A study is being made on the possible effect of alkalization on the solubility of sulfonamide crystals in the urine. From preliminary observations it appears that all patients should receive alkalies with either drug.

Dermatitis, apparently caused by the administration of these drugs, was noted in 1 patient (morbilliform rash) in the sulfadiazine group and in 2 (1 maculopapular, 1 urticarial) receiving sulfathiazole. One patient in the latter group showed a mild conjunctivitis associated with the dermatitis.

The diagnosis of psychosis as being due to the use of chemical agents is difficult to establish. However, we have encountered 10 patients (7 sulfadiazine, 3 sulfathiazole) whose cerebral symptoms were attributed by us to the drug. Although it is too early to draw any definite conclusions regarding this toxic manifestation, it appears to us that sulfadiazine tends to produce cerebral symptoms more often than sulfathiazole. The question of drug fever is also difficult to evaluate in pneumonia, although 3 patients (1 sulfadiazine, 2 sulfathiazole) developed this condition.

Repeated blood studies* showed little evidence of a marked reduction in hemoglobin, red blood cell or white blood cell counts that could be attributed to either drug. In 4 patients (2 sulfadiazine, 2 sulfathiazole) the total white cell count fell below 5000, and in 1 sulfathiazole treated patient the percentage of neutrophils dropped to 32% after 6 days of treatment. All these patients recovered and in only 1 instance was treatment stopped. There were no cases of acute hemolytic anemia in either group, but, in view of the behavior of sulfadiazine in penetrating red blood cells,⁷ such a possible complication should be anticipated.

Blood Concentrations of Sulfadiazine and Sulfathiazole. The average concentration of free sulfadiazine in whole blood⁷ as shown by daily determinations during the entire period of treatment was 8.6 mg. per 100 cc., compared with an average concentration of free sulfathiazole in plasma⁷ of 6 mg. per 100 cc. Under similar circumstances the average concentration of acetylsulfadiazine in whole blood was 1.7 mg. per 100 cc. as compared with an average concentration of acetylsulfathiazole in plasma of 2.3 mg. per 100 cc. The average proportion of total drug acetylated was 16.5% for sulfadiazine and 27.7% for sulfathiazole. These data on the different acetylation values for the two drugs are highly significant.

Comment. On the basis of mortality it appears that sulfadiazine and sulfathiazole are both effective drugs for the treatment of pneumococcal pneumonia. The mortality of 11% (corrected to 6.3%) in the sulfadiazine treated group and 17% (corrected to 11.5%) in the sulfathiazole group compare favorably when all of the factors

* Dr. W. J. Crocker, Chief of the Division of Clinical Pathology of the Laboratories of the Philadelphia General Hospital, coöperated with the authors in this phase of the work.

influencing fatality⁴ are considered. As previously stated, no sulfadiazine treated patient died when therapy was instituted within 3 days of the onset of illness (Table 5). For both drugs the average mortality for this same time limit was 3.3%. Clinical response, as evidenced by a fall in temperature was slightly more striking with sulfadiazine than with sulfathiazole.

In both therapeutic groups there was a low incidence of serious toxicity from the use of these drugs. The relatively low incidence of vomiting in both groups is especially impressive when compared to our previous experience with sulfapyridine.^{2,3,5} Microscopic hematuria was encountered more often in the patients receiving sulfathiazole and this, we believe, is related chiefly to two factors: (a) The more pronounced acetylation of the sulfathiazole molecule; and (b) the poorer solubility of acetylsulfathiazole in urine¹ as compared with acetylsulfadiazine. These two facts might readily account for a lessened irritation of the urinary tract by sulfadiazine and a consequent lowered incidence of microscopic hematuria. This impression is supported by our observation on the presence of fewer crystals in the urine of sulfadiazine treated patients.

Summary. 1. Sulfadiazine was given to 100 adult patients with pneumococcal pneumonia, and a control series of 100 patients was treated with sulfathiazole.

2. There were 11 deaths in the sulfadiazine series, 5 of which were hospitalized for less than 24 hours (corrected mortality for 95 patients, 6.3%). In the sulfathiazole series there were 17 deaths, 8 of which were hospitalized for less than 24 hours (corrected mortality, 11.5%).

3. Sulfadiazine tends to lower the temperature somewhat more rapidly than does sulfathiazole.

4. The toxic manifestations were approximately the same in the two therapeutic groups.

5. The group treated with sulfadiazine showed higher concentrations of free drug than did the group receiving equivalent amounts of sulfathiazole.

6. The average proportion of drug acetylated was 16.5% for sulfadiazine and 27.7% for sulfathiazole.

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BOOK REVIEWS AND NOTICES

HAEMORRHOIDS AND THEIR TREATMENT: The Varicose Syndrome of the Rectum. By KASPER BLOND, M.D., Vienna, Formerly First Assistant, Rothschild Hospital, Vienna; Hon. Consulting Surgeon, Municipal Hospital, Vienna, etc. Translated by E. STANLEY LEE, M.S., F.R.C.S., Hon. Assistant Surgeon, Westminster Hospital. Pp. 140. 49 illustrations, many in color. Baltimore: The Williams & Wilkins Company, 1940. Price, \$4.50.

This book propounds the interesting point of view that such diseases of the anal and perianal region as hemorrhoids, pruritus, fissure, proctitis, fistula, prolapse of the rectal mucosa are all due to what he terms "a varicose syndrome of the rectum." By this he means that there is a temporary reversal of flow in the portal circulation which permits the portal blood to flow through the superior, middle and inferior hemorrhoids to the caval circulation. This he believes is the cause of the anorectal varices which secondarily are the cause of the various lesions and diseases of this area. In the treatment of these lesions, he recommends an injection method that he terms "vein-compression." The injections are made in small doses, 1 to 2 minims in a succession of circles beginning 8 to 10 cc. above the anorectal line. He uses quinine bihydrochloride and urethane and does not attempt to thrombose vessels but simply to set up an inflammatory reaction, which will compress the superior hemorrhoidal veins and so cut off the back flow from the portal into the caval circulation.

The author recognizes that for thrombosed external hemorrhoids surgery is necessary, but anal fissures, which he describes as varicose ulcers of the anus, he injects with 1 or 2 drops of quinine-urethane solution at the base after a topical application of cocaine.

He looks upon anorectal fistula as a suppurative thrombo-phlebitis of the anorectal veins and treats these lesions also by vein compression. He believes that thrombophlebitis of the anorectal area may be the cause of many types of biliary disease and devotes a chapter to the discussion of this subject.

Although the ideas expressed and the therapies suggested differ from those in general usage, nevertheless the subject and its presentation are most interesting, especially to one interested in proctology. L. F.

THE 1940 YEAR BOOK OF PATHOLOGY AND IMMUNOLOGY. Pathology. Edited by HOWARD T. KARSNER, M.D., Professor of Pathology; Director of the Institute of Pathology, Western Reserve University, Cleveland. Immunology. Edited by SANFORD B. HOOKER, A.M., M.D., Professor of Immunology, Boston University School of Medicine; Immunologist, Massachusetts Memorial Hospitals. Pp. 688; 115 illustrations. Chicago: The Year Book Publishers, Inc., 1940. Price, \$3.00.

For some years past, physiologists and biochemists have greatly profited by the Annual Reviews of their specialties. Pathologists and immunologists have long wished for a similar annual survey of progress, and the present Year Book represents realization of their wish. Ably edited by two well-known authorities, this book will find a ready welcome. The section on pathology (pp. 1-365) deals with recent progress in general pathology, with the pathology of tumors, the pathology of the various systems of

organs, and with advances in technical methods. The chief subjects reviewed in the section of immunology (pp. 383-653) are: immunity to bacterial diseases, to viral and rickettsial diseases, to protozoa, and to tumors; there are chapters on chemotherapy, anaphylaxis and allergy, blood groups, and immunochemistry. Since pathology and immunology are basic sciences of interest to every discipline of medicine and surgery, this year book may be expected to be of great interest to others than pathologists and immunologists. The editors and publishers are to be congratulated on launching this useful work.

B. L.

CLINICAL ROENTGENOLOGY OF THE ALIMENTARY TRACT. By JACOB BUCKSTEIN, M.D., Visiting Roentgenologist (Alimentary Tract Division), Bellevue Hospital, New York City; Consultant in Gastro-Enterology, Central Islip Hospital. Pp. 652; 525 illustrations. Philadelphia, W. B. Saunders Company, 1940. Price, \$10.00.

THIS book consists of 58 chapters in which the alimentary tract, gall bladder and bile ducts, diaphragm, spleen, liver and pancreas are discussed in detail. The author has consulted most of the important literature and has discussed and illustrated many of the lesions involving those portions of the intestinal tract in which he was interested. The illustrations, published in the negative, are exceedingly good. The author has allotted more space to the small intestines than is found in any of the recent books on the gastro-intestinal tract. For this he is to be complimented as the small intestines have been largely overlooked by clinicians, gastro-enterologists and radiologists. There is still much to be learned about this portion of the gastro-intestinal tract.

This Reviewer was a little surprised that the author did not stress a standard meal more than he has, as a standard meal seems essential if radiologists are going to compare their studies. Furthermore, subjects like gastro-intestinal allergy and vitamin deficiency and physiologic motility cannot be adequately determined unless standard meals, containing no food elements or preparations facilitating suspension of the barium are used.

The Reviewer was also disappointed in not finding more discussion of the determination of tone in the unfilled stomach, and of the problem of non-opaque gastric residues in the stomach which shows slight or no delay of gastric motility. The Reviewer was also a little surprised that more consideration had not been given to the method of studying intestinal obstruction devised by T. Grier Miller and W. O. Abbott—one of the really important contributions to medicine of recent years.

In spite of the above comments this book is a distinct addition to our knowledge of these subjects and the author has done a magnificent piece of work. His subject matter has been arranged in a perfectly logical manner and the publishers have given him a good paper on which the print stands out well and the paper is not too glossy. This book should be an acceptable addition to the libraries of clinicians, gastro-enterologists and radiologists.

E. P.

HYDROCEPHALUS. Its Symptomatology, Pathology, Pathogenesis and Treatment. By OTTO MARBURG, M.D. Pp. 217; 28 illustrations. New York, Oskar Piest, 1940. Price, \$3.00.

HERE is brought together such important literature as already exists, to which is added the author's personal experience. It is believed hydrocephalus results from disturbance of water metabolism, the ventricles are enlarged, communications obstructed and in this way the disease is produced. Treatment must be directed toward changing the permeability of the blood-vessel walls and the barriers, and of the water metabolism. Important chapters are Etiology and Occurrence, Symptomatology and Syndromes, and Treatment. The last includes healing *per se*, medical

treatment, x-ray treatment, spinal puncture, cisternal and ventricular puncture, lasting drainage—callosal puncture, plexectomy, ligature of the carotids and decompressive trepanation. This is an interesting monograph; after reading it one has the impression that the treatment of hydrocephalus is still to be largely experimental. The bibliography covers 24 pages.

N. Y.

MAN'S GREATEST VICTORY OVER TUBERCULOSIS. By J. ARTHUR MYERS, Ph.D., M.D., F.A.C.P., Professor of Medicine and Preventive Medicine and Public Health, University of Minnesota, and Chief of Medical Staff, Lymanhurst Health Center, Minneapolis. Pp. 419; 31 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, \$5.00.

DR. MYERS has written a book for the veterinary medical profession on the control of tuberculosis in cattle, but with the perfectly obvious secondary if not actually primary aim of inspiring physicians and public health officers, through the example afforded, to renewed effort for the conquest of tuberculosis in man. In constructing the volume he has not felt bound by the title to limit its contents strictly to the subject of bovine tuberculosis, but has allowed himself wide latitude for the discussion of other triumphs of veterinarians and for much general information on tuberculosis in man. All of this adds to the value of the book. The veterinarian will find it an uncommonly successful source book for ready reference on the half century of bovine tuberculosis control, and will find it almost equally useful for technical information on tuberculosis. A unique feature is the assemblage of a series of short, biographical sketches of the lives of the veterinarians who have played a part in tuberculosis control.

In one sense it is a historical volume, but it uses the historical method as an object lesson rather than as an end in itself. The early successes and many early shortcomings and failures in tuberculosis control are noted at length; but the historical account leads quite directly to a detailed presentation of the existing bovine antituberculosis program. The drive in earnest, with eradication not mere control as an objective, began in 1917. The campaign of the Bureau of Animal Industry was simple in theory, although harassed by many difficulties in practice. Chapter XXII gives an inspiring picture of the persistence of the Bureau chiefs, and the final "accrediting" of the 48 states.

As in Dr. Myers' other books, each chapter ends with a concise summary. The method affords the reader a quick view of the entire subject. The summaries are concise and highly informative. The book is well illustrated and the press work is excellent.

E. L.

PSYCHIATRIC SOCIAL WORK. By LOIS MEREDITH FRENCH, Director, Study of Trends, American Association of Psychiatric Social Workers; Psychiatric Social Worker and Instructor in Mental Hygiene, New Jersey State Teachers College at Newark. Pp. 344. New York: The Commonwealth Fund, 1940. Price, \$2.25.

In this pioneer volume by Mrs. French, the effort is to describe psychiatric social work, what its workers do, and the relation it bears to psychiatrists, social agencies and the community. The present organization had its incipency in 1920, and today there are about 500 members. It has served under different names and its future is somewhat uncertain. In 1935, 46% of its members were working in agencies that were a combined psychiatric and social service; in 1936, the percentage was 49; in 1937, 54; and in 1940, approximately 50%, thus receding to that of 14 years ago.

On 13 scattered pages there are attempts at definition of this work, and on 8 other pages, the difficulties attending such definition are mentioned. Where the service operates in general hospitals with an associated psy-

chiatric clinic, it operates efficiently; but where the effort is a study of emotional problems that may be found in any clinic, conflict arises between the psychiatric and medical approach. A bibliography of 14 pages and a helpful index are included. N. Y.

THE ENDOCRINE FUNCTION OF IODINE. By WILLIAM THOMAS SALTER, Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Thorndike Laboratory, Boston City Hospital. Pp. 351; 40 figures and 45 tables. Cambridge, Mass.: Harvard University Press, 1940. Price, \$3.50.

THIS is an admirable survey, containing a wealth of data from the literature and from the author's investigations, and analyzed with critical discernment. It includes discussions of iodine balance and endocrine balance, "labeled" radioactive iodine in the study of thyroid function, iodine in relation to endocrine glands other than the thyroid, clinical problems of iodine medication in thyroid disease, laboratory methods, and many other problems of iodine metabolism and thyroid function. The author puts various isolated facts into relationship to each other, and makes of these separate findings a reasonable whole. He writes in a delightfully readable style. Undoubtedly this book will be enthusiastically read by both investigators and practising physicians. I. Z.

RELATION OF TRAUMA TO NEW GROWTHS. Medico-Legal Aspects. By R. J. BEHAN, M.D., Dr. Med. (Berlin), F.A.C.S., Surgeon, St. Joseph's Hospital and Dispensary, City of Pittsburgh Hospital at Mayview, The Tuberculosis Hospital at Leech Farm, and the Allegheny County Hospital at Woodville. Pp. 425. Baltimore: The Williams & Wilkins Company, 1939. Price, \$5.00.

ANY expert who is called upon to express an opinion regarding the rate of trauma as related to the onset of malignancy must be acquainted with this book. It is an essential addition to the library of surgeon, orthopedist and pathologist. G. W.

IMMUNE-BLOOD THERAPY OF TUBERCULOSIS. With Special References to Latent and Masked Tuberculosis. By JOSEPH HOLLOS, M.D. Pp. 195. Boston: Bruce Humphries, Inc., 1938. Price, \$2.50.

CAREFUL perusal of this book leaves the Reviewer interested but skeptical. H. H.

STUDIES FROM THE CENTER FOR RESEARCH IN CHILD HEALTH AND DEVELOPMENT, SCHOOL OF PUBLIC HEALTH, HARVARD UNIVERSITY. (Monographs of the Society for Research in Child Development.) Washington, D. C.: Society for Research in Child Development, National Research Council, 1939.

TYPES, LEVELS, AND IRREGULARITIES OF RESPONSE TO A NURSERY SCHOOL SITUATION OF FORTY CHILDREN OBSERVED WITH SPECIAL REFERENCE TO THE HOME ENVIRONMENT. (Vol. IV, No. 2, Serial No. 21, Price, \$1.25.) By ELEANOR SLATER, with the assistance of RUTH BECKWITH and LUCILLE BEHNKE. Pp. 148; 7 illustrations and 15 tables.

IN the course of a comprehensive study of child development which is in progress at the Harvard School of Public Health, the reactions of 40 children to life at a nursery school were studied. The number of changes in play, the number of contacts with other children, and of contacts with adults, the number of words spoken in 125 minute periods and various other aspects of behavior which could be recorded objectively were studied. A study of these factors from day to day showed definite trends. Some of the children were more inhibited at the beginning, some were accelerated at first and some fluctuating. One of the most interesting observations was that

the upper third of the group according to intelligence tests were the most inhibited upon entering the school.

An attempt was made in 13 cases to examine the behavior in the nursery with reference to home conditions. Changing conditions at home were associated in many instances with marked irregularities in the responses observed in the nursery. The authors however state that "a small child is subject to too many stresses both outside and within himself to make one able to isolate any one factor as primarily responsible for any changes in behavior or symmetry of development."

THE PHYSICAL AND MENTAL GROWTH OF GIRLS AND BOYS AGE SIX TO NINETEEN IN RELATION TO AGE AT MAXIMUM GROWTH. (Vol. IV, No. 3, Serial No. 22, Price, \$2.00). By FRANK K. SHUTTLEWORTH. Pp. 291; 150 illustrations and 110 tables.

ON the basis of data collected on 747 girls and 711 boys under the direction of Professor Walter F. Dearborn, the author has presented detailed analysis—152 graphs and 110 tables—of 9 dimensions, erupted teeth and intelligence test data in relation to "MG-age" or age at the close of the year of maximum growth in standing height. This classification provides an interesting method of grouping individuals with similar patterns of physical growth, probably due to the timing of underlying endocrine factors, since a previous study had shown a high correlation between menarcheal age and age at maximum growth in standing height.

He has found that early MG-age groups are consistently bigger than the late MG-age groups up to the age of 12 for girls and 14 or 15 for boys, but that these differences tend to disappear or are reversed at later ages. When growth curves are plotted not to chronological age but arranged with significant points in the same vertical line, the slopes of the different groups are similar although differing in intensity, and the slope for each dimension has its own characteristics. Early MG-age groups attained their 28 teeth a little sooner and are found by intelligence tests to be brighter than the late MG-age groups. In concluding, the author postulates a theory of physical growth emphasizing the influence of hereditary stature factors in cancelling the differences created by variation in the timing of endocrine stimulation.

This is probably the most complete study of the subject ever published and furnishes a tremendous amount of reference material for those who are studying the growth of children.

EVALUATIONS OF ADOLESCENT PERSONALITY BY ADOLESCENTS. (Vol. IV, No. 4, Serial No. 23, Price, \$1.00.) By CAROLINE McCANN TRYON. Pp. 83; 12 illustrations and 15 tables.

To discover qualities or aspects of personality which children consider desirable in each other, 350 children in the high sixth and low seventh grades of Oakland public schools, whose average age was 12 years, were given booklets with 20 pairs of attributes (*e. g.*, restless and quiet, leader and follower, and so forth) and asked to write down the names of their classmates who seemed to be described. Three years later the same group in the high ninth grade were given the same tests, when their average age was 15 years.

The material obtained has been analyzed statistically and the graphic presentation of correlation profiles shows clearly the close relationship of certain traits: such as "popular, good-looking, friendly, enthusiastic" for the 15 year old boys. It is shown that values for boys change little from the age of 12 to 15 years with prestige being determined by physical skill, aggressiveness and fearlessness, although being unkempt becomes an undesirable characteristic of older boys. Changes for the girls are more marked "with emphasis shifting from being lady-like and conforming with adult standards to being a good sport and attractive to boys."

This monograph furnishes many interesting glimpses into the thoughts of the adolescent.

T. R.

NEW BOOKS.

The Therapy of the Neuroses and Psychoses. A Socio-Psycho-Biologic Analysis and Resynthesis. By SAMUEL HENRY KRAINES, M.D., Associate in Psychiatry, University of Illinois, College of Medicine; Assistant State Alienist, State of Illinois, etc. Pp. 512; 3 figures. Philadelphia: Lea & Febiger, 1941. Price, \$5.50.

Radiology Physics. An Introductory Course for Medical or Premedical Students and for all Radiologists. By JOHN KELLOCK ROBERTSON, F.R.S.C., Professor of Physics, Queen's University, Kingston, Canada. Pp. 270; 188 illustrations. New York: D. Van Nostrand Company, Inc., 1941. Price, \$3.50.

Age Morphology of Primary Tubercles. By HENRY C. SWEANY, M.D., Medical Director of Research, Municipal Tuberculosis Sanitarium, Chicago, and Research Associate, Department of Physiology, University of Chicago. Pp. 265; 75 plates and 26 charts. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.00.

Debatable Tumours in Human and Animal Pathology. By W. F. HARVEY, E. K. DAWSON, and J. R. M. INNES. From the Research Laboratory of the Royal College of Physicians, Edinburgh, The Cancer Control Organization of Edinburgh and South-East Scotland, and the Institute of Animal Pathology, University of Cambridge. (Cancer Research, Ltd., 1940.) Pp. 124; 40 plates. Edinburgh: Oliver & Boyd, Ltd., 1940, for the Cancer Control Organization of Edinburgh and South-East Scotland. Price, 10/6.

The American College of Physicians. Its First Quarter Century. By WILLIAM GERRY MORGAN, M.D., LL.D., Sc.D., M.A.C.P., Historian; Professor of Gastro-enterology and Emeritus Dean, Georgetown University School of Medicine, Washington, D. C. Pp. 275; illustrated. Philadelphia: American College of Physicians, 1940. Price, \$2.00.

This is a valuable record of the first 25 years in the existence of an important medical organization, with particular interest for those especially concerned with its welfare. It gives a chronologic account of the existence of the College, biographic sketches of its important officers, and in the latter half of the book a "Chronology" extracted from the minutes of the College meetings.

Diseases Affecting the Vulva. By ELIZABETH HUNT, B.A., M.D., CH.B. (LIVERP.), Honorary Physician to the Skin Department, South London Hospital for Women; Honorary Dermatologist, New Sussex Hospital for Women and Children, Brighton, etc. Pp. 215; 36 illustrations and 18 plates in color. St. Louis: The C. V. Mosby Company, 1940. Price, \$4.50.

The Journal of Clinical Endocrinology, Volume 1, No. 1, January, 1941. Issued Monthly for The Association for the Study of Internal Secretions. Pp. 90; illustrated. Springfield, Ill.: Charles C Thomas, 1941. Price, Annual subscription, \$6.50; single copies, \$1.00.

Manual of Physical Diagnosis with Special Consideration of the Heart and Lungs. By MAURICE LEWISON, M.D., Professor of Physical Diagnosis, University of Illinois College of Medicine; Consulting Physician, Cook County Hospital, etc., and ELLIS B. FREILICH, M.D., Associate Professor of Medicine, University of Illinois College of Medicine; Professor of Medicine, Cook County Graduate School of Medicine, etc. In Collaboration with GEORGE C. COE, M.D., Instructor of Medicine, University of Illinois College of Medicine; Associate Physician, Cook County Hospital; Clinical Assistant, Mount Sinai Hospital, Chicago. Pp. 317; 75 illustrations. Chicago: The Year Book Publishers, Inc., 1941. Price, \$3.00.

Hospital Formulary and Compendium of Useful Information. University of California. Pp. 270. Berkeley, Calif.: University of California Press, 1941. Price, \$2.00.

Tumores Primitivos Malignos Bronco-Pulmonares. Cancer, Sarcoma, Linfogranuloma. (Vol. III, Biblioteca Argentina de Medicina Interna.) By JULIO PALACIO, Adjunct Professor of Clinical Medicine in the Medical Faculty of Buenos Aires; Director of the Municipal Dispensary for Respiratory Tract, and EGIDIO S. MAZZEI, Adjunct Professor of Medicine in the Medical Faculty of La Plata; Chief of Clinic in Professor Castex's Department; Chief of the Section on Human Pathology of the Research Institute. Pp. 401; 129 illustrations and 4 colored plates. Buenos Aires: "El Ateneo," 1940.

The Periodicity and Cause of Cancer, Leukemia and Allied Tumours, with Chapters on Their Treatment. By J. H. DOUGLAS WEBSTER, M.D., F.R.C.P.E., F.F.R., Honorary Director, Meyerstein Institute of Radiotherapy, Middlesex Hospital, London; Lecturer and Examiner in Radiology, University of London; Examiner in Radiotherapy, Faculty of Radiologists, London, etc. Pp. 178; 6 charts, and 5 plates. Baltimore: The Williams & Wilkins Company, 1940. Price, \$3.50.

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PROGRESS OF MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF

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OVARIAN TUMORS.

WHEN one is confronted with an obvious ovarian tumor, it is of much help to have some statistical information as to the relative incidence of the various types of tumors, their symptomatology and probability of malignant change as can be analyzed from a large series of tumors of all types. In a study of 1101 ovarian tumors presented by Bernstein,¹ it was found that the simple and dermoid cysts were first and second in order of incidence. Papillary serous cancer was third, constituting 80 % of all ovarian cancers and being four times more frequent than the benign serous cystadenoma. In this series, 17.3 % of all ovarian tumors were malignant, 95 % of these being cancer and 5 % being sarcoma. Fifty-eight per cent of all ovarian tumors are in patients between 20 and 40 years, 30 % are over 40 years and 12 % under 20 years. Normal menses occur in over half of the patients with ovarian tumors, hyperfunctional bleeding in about one-quarter and hypofunctional bleeding in about 18 %. In 58 % of menopause patients malignancies were found, while metastases were noted at operation in 76 % of the patients with ovarian cancer, 80 % of these being due to papillary serous cystadenocarcinoma. Pain constitutes 44 % of all symptoms and is present in 75 % of the patients, but is usually not severe even in the late stages and is 25 % more frequent among the benign tumor cases. Nausea and vomiting constitute only 19 % of the complaints, being present most frequently in the benign tumor cases. Of all the cases there was bilateral involvement in 21 %, but of the malignant cases alone the involvement was bilateral in 55 %. In brief, therefore, when a patient past the menopause has a bilateral ovarian tumor which causes little pain, malignancy must be strongly suspected.

In order to understand how ovarian tumors are formed it is necessary to study the development of the ovary which has been well summarized by Geist² who reminds us that early in the development of the gonad the surface epithelium of the anlage of the ovary becomes many layered and extends downward into the mesenchyme as solid cell cords. This

represents the indifferent gonadal stage but rapidly passes into that of the definitive sex gland. In the male, the cell cords form the tubular system and possibly the interstitial cells, while in the female they become the undeveloped granulosa and theca interna cells, which later are utilized in the development of the Graafian follicle, although some recent observers believe that the granulosa and theca cells are derived from the mesenchyme. In addition to the two cell types mentioned, there remain in the female gonad remnants of structures that achieve full development only in the male and are identified as cords and tubules in the region of the rete ovarii. These structures usually remain quiescent but may develop and function in a male direction. Occasionally gonads are encountered that are functionally inefficient and may not develop either along male or female lines. With this brief preface we shall mention the four types of tumor which have been of so much interest of late, although each type will be considered in more detail later.

The granulosa cell tumor arises from unused granulosa cell forerunners in the ovary. These tumors store or produce estrogenic hormone and affect the host by exaggerating certain aspects of the female physiology.

The theca cell tumor arises from the forerunners of the theca interna cells and in their biologic aspect are similar to the granulosa cell tumor, but are commonly found in the postmenopausal period.

The arrhenoblastoma arises from male-directed elements which have remained quiescent in the ovary and presumably contain a male sex hormone. They affect the host by causing a defeminization with the development of a male hair type, male gait, voice and larynx.

The dysgerminoma arises from neuter cells of germinal epithelial origin. It has no incretory function and no pathologic physiologic effect on the host, but is found often in individuals with defective gonads and atypical somatic development.

Granulosa Cell Tumor. According to Schulze¹⁷ the clinical picture of granulosa cell tumor is sufficiently definite to allow of preoperative diagnosis, particularly in the preadolescent and postmenopausal groups. The prognosis of these tumors cannot be considered settled as most of the cases in the literature are reported without adequate follow-up, and a number of cases of late recurrences have served to upset somewhat the former idea of a very low rate of malignancy in these tumors. The clinical picture of these tumors, aside from certain mechanical effects which might be due to any type of ovarian tumor, is due to excess estrogenic activity of the growth. In children, there is precocious puberty, in postmenopausal women, rejuvenation with a resumption of cyclic or irregular uterine bleeding, swelling of the breasts with occasional galactorrhea and restoration of a youthful type of vaginal mucosa. In the adult premenopausal woman, irregular, profuse and prolonged bleeding alternating with periods of amenorrhea is characteristic. A glandular cystic type of hyperplasia of the endometrium has been found in a high proportion of cases where it has been examined. Sterility is theoretically to be expected through inhibition of the pituitary and secondarily of the remaining ovary by the hyperestrinism produced by the tumor. One of Schulze's patients had been sterile for 5 years, yet delivered a normal child 2 years after operation without other treatment for the

sterility. The question of the radiosensitivity of granulosa-cell tumors is not settled. Most of the reports of inoperable, incompletely removed or recurrent tumors which have disappeared under Roentgen ray treatment have been made too soon to know what the final outcome will be. A recurrence of bleeding following adequate radiation treatment for supposed functional menorrhagia, however, should certainly warrant further study of the patient, bearing in mind the possibility that a small unrecognized granulosa-cell tumor might be present. In spite of the relatively high rate of malignancy reported in some series, Schulze believes that the proportion of cures in cases adequately followed is still very great unless there was definite evidence of malignancy at the time of operation and therefore conservative operation is indicated in young women, although they should be followed for a long time to guard against late recurrences.

Bland and Goldstein² are also of the opinion that these tumors are not very malignant. They have studied a series of 160 cases in 96 of which the final outcome is known; 42 were well for periods of from 1 to 10 years following operation, while 20 patients were dead, 4 of them dying from metastases within one year after operation. The same opinion is expressed by Dockerty and MacCarty^{6a} of the Mayo Clinic where 30 of these tumors have been encountered including one that weighed 34 pounds. They have found that these tumors cause a hyperplasia of the uterus with a thick, boggy, proliferative type of endometrium often containing cysts. In their experience 90% of these tumors are unilateral, 90% are solid and 90% are of a low grade of malignancy. They are usually well encapsulated, the cut surface has the homogeneous, granular appearance of liver sausage which allows one to make a correct gross diagnosis in 50% of the cases. Of the 30 cases, 25 are living and well from 2 to 30 years after operation.

There has been considerable confusion in the differentiation of granulosa and theca cells in some instances, and Traut and Marchetti¹⁹ state that such differentiation is never easy and in some cases may be impossible. However, they call attention to the fact that comparatively little work has been done with the aid of silver impregnation methods and they believe that the Foot silver stain has never been used in connection with granulosa and theca neoplasms. They state that this technique has many advantages. It not only reveals the argentaffine characteristics of reticular and cellular cytoplasm, but it also gives a finely graduated tonal differentiation of all the cells. Neoplastic granulosa cells occur in islands consisting of from a few to several hundred cells, seldom existing singly. These islands are surrounded by strands or networks of reticulum carrying with them numerous theca cells and the vascular supply. The nuclei of theca and granulosa cells are impossible to distinguish from one another, as they contain similar nucleolar and chromatin bodies. However, the cytoplasm of the granulosa cells contains many argentophile granules, whereas the cytoplasm of the theca cell is almost devoid of these bodies. In addition, the theca cell is always in intimate relationship to the reticular framework to such a degree that each cell is surrounded by a capsule of this material which isolates it from its neighboring theca cells. In contrast, the granulosa cells exist in groups, usually of large numbers, each cell being in immediate contact with its neighboring granulosa cells. The complete

island of granulosa cells is surrounded but not penetrated by the reticulum. The application of these differential points makes it possible to analyze the Graafian follicle tumors as to their content of these two types of cells. They state that so-called granulosa cell tumors contain varying amounts of theca cell elements as well, so that pure granulosa cell tumors are rare. Most tumors contain from one-fourth to one-third of their differentiated cells in the form of theca cells and, on the other hand, most so-called theca cell tumors also contain granulosa cell elements in considerable numbers.

Theca Cell Tumors. Since there have been reported only about 25 examples of this tumor it must be considered rare. In reporting a series of 10 cases Dockerty^{5a} states that there are three theories to explain the origin of these tumors. In the first theory they are believed to be derived from the ovarian stroma and are regarded as luteinized fibromas. A second theory holds that they are luteinized granulosa cell tumors and that they should not be called "theca cell tumors." The third theory states that these tumors arise from theca cells and represent a separate entity. The clinical features usually associated with theca cell tumors resemble closely those found in association with granulosa cell tumors of the ovary. More than 80 % of the neoplasms occur after the menopause and produce vaginal bleeding which may or may not be periodic, although some tumors produce no menstrual abnormalities. The tumors are fibrous, solid, usually encapsulated and canary yellow in color. On section, the "liver sausage" consistency of granulosa cell tumors is lacking and, except for the yellow color, a diagnosis of fibroma would seem justified on the basis of gross inspection. A thin "rind" of ovarian tissue can usually be shelled from the surface of the tumor in the form of a smooth capsule. Histologically, the cardinal features are the predominance of plump, fusiform cells with vacuolated cytoplasm and oval nuclei. It is generally conceded that they are of a low grade of malignancy.

Commenting upon these tumors, Collins, Varino and Weed³ state that they vary in size from a few centimeters in diameter to the size of a large grapefruit. On vaginal examination the consistency is that of a fibroma of the ovary. The tumor is usually unilateral, may occur at any age, the oldest reported case being a woman of 90 and the youngest, 18 years old. All but 3 of the reported cases occurred at or past the menopause and are usually accompanied by atypical bleeding. In younger women, periods of amenorrhea, preceded or followed by menorrhagia, is the usual history. They believe that in the past many of these tumors have been reported as fibromas of the ovary. In the 2 cases which they have seen unilateral oöphorectomy was performed and, since removal of the tumors, normal menstrual cycles have been established in both cases.

Arrhenoblastoma. In contrast to the granulosa cell and theca cell tumors which have been described as feminizing, the arrhenoblastoma is a masculinizing tumor and it is quite a rare one, but like the other tumors previously described it is of a low grade of malignancy. Novak¹⁴ states that this tumor occurs most frequently in relatively young patients, the decade between 20 and 30 showing the largest incidence. The defeminizing phenomena associated with this tumor consist of amenorrhea, retrogression of the mammary glands and loss of the femi-

nine contour, while the masculinizing effects consist of hirsutism, deepening of the voice and hypertrophy of the clitoris. Removal of the tumor is followed by a return to normality although this may not always be complete. Histologically, all gradations are seen between a structure closely simulating that of normal testis (testicular adenoma) to pictures showing only incomplete efforts at tubular formation, to those of sarcoma-like appearance. The rarity of the tumor may be judged from the fact that Dockerty and MacCarty⁶⁶ are able to present but 4 cases from the Mayo Clinic over a period of 26 years. They state that in the presence of a palpable pelvic tumor, associated with the masculinizing syndrome, a diagnosis of arrhenoblastoma seems justified. However, basophilic pituitary adenomas, pinealomas and adrenal cortical tumors may be associated with a similar clinical picture. Certain features help in distinguishing between them. Hypertension, a cardinal symptom of adrenal and pituitary neoplasms, is unusual in cases of arrhenoblastoma. A definite increase in weight with a "buffalo" distribution of fat is associated frequently with an adrenal or pituitary neoplasm but may occur with an ovarian tumor. Pituitary changes of a hyaline nature have been encountered in cases in which death has occurred owing to arrhenoblastoma, which leads them to ask whether or not this master gland may not be the basis of secondary sex changes. Granulosa cell tumors offer the only difficulty in making a differential diagnosis histologically. The pathologic characteristics of both tumors have a certain similarity but interstitial cells are absent in granulosa cell neoplasms and tubular structures are almost never observed. Malignancy in an arrhenoblastoma is shown by the usual criteria of multiple mitotic figures, irregularity in the size and staining properties of the nuclei and local invasion. It can be recognized in fresh sections of tumor tissue and, when present, warrants radical operation. Treatment, especially among younger individuals, should otherwise be conservative.

Dysgerminoma. The term "dysgerminoma" refers to a rare type of ovarian tumor which had formerly been called by a variety of names such as seminoma, embryoma, sex cell carcinoma and large round cell carcinoma. In presenting a paper which reviews 79 cases collected from the literature, Seegar¹⁸ states that there are several clinical features which aid in arriving at a preoperative diagnosis of dysgerminoma, particularly the duration of symptoms and the age and sexual development of the patient. The occurrence of a large solid tumor in the ovarian region in a girl past puberty is suggestive of such a diagnosis. The duration of abdominal pain and swelling which are the principal symptoms, is usually about 6 months. There is a frequent association of this tumor with pseudohermaphroditism, hypogenitalism and other forms of sexual maldevelopment, such as infantilism, amenorrhea, delayed onset of menstruation and sterility, but the absence of such abnormalities is of no diagnostic significance. Extensive infiltration of the rectum or the bladder with involvement of the retroperitoneal lymph nodes occurs with the more malignant tumors, but metastasis to other organs is rare. The outstanding gross pathologic features of this tumor are the firm or elastic consistency, the nodular surface and the large size, often in excess of 2000 gm., suggesting rapid growth. The cut surface is granular and glistening and the more dense stroma-

togenous areas are widely separated. Microscopically, the cells of the tumor stand out individually, suggesting the appearance of caviar, especially in the frozen section. The cells are large and discrete and are arranged in nests and strands, with a moderate amount of clear cytoplasm which takes the eosin stain and with large hyperchromatic nuclei. One of the more constant characteristics of the microscopic structure is the lymphoid infiltration of the stroma. In Seegar's experience the degree of microscopic differentiation cannot be relied on in distinguishing a benign from a malignant tumor, and similarly the appearance of gonadotropic substance in the urine is unreliable as a guide to prognosis because of the scarcity of such determinations to date. Of the cases in this series in which there were adequate follow-up data, approximately 50% have remained well beyond 5 years. The treatment of choice for dysgerminoma is excision of the tumor, the uterus and the opposite ovary being left intact. The preservation of the child-bearing function is desirable for the patients, who are usually young adults. For patients showing hermaphroditism or sexual underdevelopment the possibility of future pregnancy is usually of no importance. For patients showing a recurrence of the tumor in the regional lymph nodes after a primary excision, irradiation or a second excision is indicated. Only 2 cases have been recorded in which a recurrence has occurred in the remaining ovary, while in 6 cases in which only the affected ovary was removed, the patient subsequently gave birth to a healthy child. This would seem to warrant the slight risk of recurrence in the opposite ovary which is assumed when conservative excision is practiced.

Commenting upon these tumors, Novak and Gray¹⁵ state that since they arise from cells dating back to the undifferentiated phase of gonadal development, it is not surprising that an exactly similar tumor, the well-known seminoma, occurs in the testis. Moreover, since it is made up of sexually indifferent cells, the dysgerminoma exhibits no endocrine activity, thus differing from the feminizing granulosa cell tumor and the masculinizing arrhenoblastoma. While dysgerminoma is often observed in sexually underdeveloped or pseudohermaphroditic individuals, it has nothing to do with the production of these abnormalities, which persist even after the removal of the tumor. While the tumor is undoubtedly malignant, there are marked variations in the degree of malignancy of individual tumors. The outlook is very favorable when the tumor is unilateral with intact capsule, but much less favorable when the capsule has been broken through, with extensive infiltration of surrounding organs. They believe, therefore, that conservative unilateral operations should be limited to unilateral growths in which the capsule of the tumor is intact and in which there is no evidence of infiltration or metastasis, while in all other cases removal of both ovaries and uterus would seem preferable. In regard to the use of postoperative irradiation after a conservative unilateral operation, they advise against such a procedure, because such treatment, by destroying the function of the conserved ovary, is as radical as a complete operation in abolishing the reproductive function, the preservation of which is the chief justification of the conservative operation. If future reproduction is to be disregarded, the complete operation followed by radiotherapy would be safer and more desirable than unilateral removal plus radiotherapy.

Brenner Tumor. A rare ovarian tumor which was first described by Brenner in 1908 has been studied from the material available at the Mayo Clinic by Dockerty.^{5b} These tumors resemble fibromas, but microscopically they contain scattered islands of pale-staining squamous epithelial cells in a dense stroma of connective tissue and Brenner called the tumor "oöphoroma folliculare." Three theories have been advanced to explain the formation of these tumors. According to the first theory (Robert Meyer) the neoplasm arises from metaplasia of the epithelium of the Muellerian ducts; the second theory (Schiller) postulates a dislocation of cells from the primitive urogenital connection, while the third theory holds that these tumors represent one-sided development of teratomas. The Brenner tumor is nearly always unilateral, varying in size from tiny nodules to masses 20 cm. in diameter. It resembles ovarian fibroma in being grayish-white and in the solid variety it is dense and hard. In another group, the tumor appears as a solid nodule growing from the wall of a cyst. Adhesions are infrequent and metastasis has not been observed. Microscopically, the picture consists of islands of squamous epithelial cells in a dense stroma of fibrous tissue. The peripheral rows of cells in these islands are frequently palisaded. Some are cystic with an inner lining of columnar cells and in some instances these cysts contain a substance which stains positively for mucus. Mitotic figures are not observed. The tumor must be distinguished from the granulosa cell tumor and also from metastatic squamous cell carcinoma, which is simple when the Galantha stain for mucus is employed. The clinical features of Brenner tumor are those of a slow growing pelvic tumor with none of the usual features of clinical malignancy. Sixty per cent of the neoplasms occur after the menopause. In discussing this study, Counseller⁴ states that while the interest in these tumors is chiefly one of histogenesis, certain factors give it surgical importance. It is not a malignant tumor and has no effect on endocrine systems. It can be cured by unilateral removal of the adnexa but it must be distinguished from the other unusual neoplasms of the ovary such as granulosa cell tumor, arrhenoblastoma and dysgerminoma, in which the surgical treatment may not be the same. The identifying features in the gross appearance usually can be detected by the experienced gynecologist and the correct diagnosis made immediately from a frozen section. Panhysterectomy is not necessary to cure this tumor, but before the tumor became definitely established pathologically, panhysterectomy was the usual procedure since it was thought to be a malignant condition. Surgically, it is important to separate this tumor from metastatic lesions of the ovary since the prognosis and surgical procedure would vary considerably in the latter type.

Krukenberg Tumor. These interesting tumors are secondary to carcinoma elsewhere, usually in the gastro-intestinal tract. In their paper on this subject, Novak and Gray^{15b} call attention to the false idea that some investigators have to the effect that all ovarian cancers secondary to gastro-intestinal cancer are Krukenberg tumors, but they insist that only those tumors, whether secondary or primary, which assume the characteristics first described by Krukenberg should be classified under this heading. The characteristics of the true Krukenberg tumor are, grossly, firm solid growths, usually of moderate size, almost always bilateral, and retaining the general shape of the ovary. The external

surface is smooth, with well developed firm capsule, with no tendency to become adherent to surrounding structures. On section some parts are quite firm, others finely spongy, some areas often degenerated, hemorrhagic or cystic, while areas of gelatinous appearance are common. Microscopically, the epithelial elements may occur as clusters of well marked acini showing various degrees of mucoid epithelial change which may be so extreme that the epithelial cells are completely melted down, leaving only the shadows of the original gland framework. The mucoid material may break through the gland wall and permeate the surrounding stroma, so that differential staining may reveal mucin not only in the glands but also in the stroma. The mucoid changes described explain the occurrence of usually large numbers of signet cells, in which the nucleus is flattened out against the cell wall by the accumulated secretion within the cell. It is these cells which have been most stressed in the microscopic diagnosis of these tumors, and which have suggested for them the designation of carcinoma mucocellulare. It would seem that this neoplastic type is brought about by the development of a primarily mucoid adenocarcinoma in the ovarian environment, or by the acquisition of mucifying tendencies by metastatic tumors which at their original site give no indication of mucoid characteristics. Such a course is not the invariable one pursued by gastro-intestinal cancers metastasizing to the ovary, since the great majority of such secondary growths develop as non-mucoid carcinomas, with the usual pattern of adenocarcinoma, so that they cannot properly be considered Krukenberg tumors. In view of the secondary character of this tumor, examination of the ovaries should never be omitted at operation for pyloric or other gastro-intestinal cancers in women. On the other hand, the gynecologist should explore the stomach and other abdominal viscera before proceeding with operations for ovarian cancer so that useless operations will be avoided. While the majority of these cancers are secondary, Novak and Gray believe that there is strong evidence for a primary origin in the occasional case, since in several cases reported the tumors were quite typical but there was no evidence at operation of a primary tumor elsewhere, none developed after the operation and the patients were in good health several years after operation. The prognosis in the common secondary cases is practically hopeless.

Concerning the frequency of these tumors, Kleine¹⁰ of the gynecologic clinic at Heidelberg found that among 176 malignant tumors of the ovary observed over a 26-year period, 16 % were Krukenberg tumors, which is distinctly higher than the usual percentage reported in the literature. There were 53 metastatic ovarian cancers but only 28 (53 %) of these were of the Krukenberg variety with typical seal ring cells. No case of primary tumor was observed, all being secondary to cancer of the gastro-intestinal tract. In 88 % of the cases the tumors were bilateral. The younger patients presented the largest tumors, up to the size of a man's head, while in patients at the menopause the tumors were usually small. In 60 % of the patients there were menstrual symptoms, usually in the form of amenorrhea following destruction of the ovarian tissue.

Struma Ovarii. In discussing tumors of the ovary which contain thyroid tissue, known as struma ovarii, Emge⁷ states that the histogenesis is obscure, but it is reasonably certain that they are not the

result of thyroid metastases into an ovary, since this is contrary to the behavior of metastasizing thyroid neoplasms. The actual incidence of these tumors is not known, but casual statistics place it at from 2 to 15% of ovarian teratomas, mainly dermoids. An ovarian struma, even though small, can unbalance the metabolism of the body and at times invade other tissues of the body by metastasis. Most of these tumors are silent unless mechanical difficulties arise and are usually not diagnosed until they reach the laboratory. They frequently come to operation without critical metabolic studies and milder types of hyperthyroidism are undoubtedly overlooked. Most ovarian strumas are benign tumors and are more common after maturity. When part of an ordinary teratoma they may not be encapsulated but may freely intermingle with other tissue. When encountered as a so-called pure struma they always have a capsule formed by mesoderm derivatives. Generally they tend to develop into a colloid goiter rather than to maintain hyperplastic activities. About 5% of these tumors may be expected to metastasize, usually to abdominal viscera.

Carcinoma. In reviewing over 100 cases of primary cancer of the ovary, Lynch¹¹ was struck by the insidious character of the disease. The first symptoms may be comparatively trivial and yet the tumor is found to be inoperable. When compelling symptoms are present, pain is the most common, usually mild at first, gradually increasing in severity. When the pain is epigastric, there is often nausea and vomiting. Menstrual disturbances are variable but may consist of postmenopausal bleeding. Of the 62 patients who were treated more than 5 years before the date of the study, there was a cure rate of 35% which should be gratifying, but Lynch is not at all satisfied after careful evaluation of the figures. Many of the patients have been re-operated or re-radiated during a period in which they should not be re-treated but merely observed. Furthermore, some of the slowly growing tumors that have been re-treated might have been still present but unrecognized on examination after 5 years, yet later they might develop and cause death. The cure rate depends largely upon the number of slowly growing tumors in the series and therefore he believes that it is useless to evaluate any method of treating ovarian cancer unless the patient has been followed for a minimum of 10 years from the date of the last treatment. He believes that the profession credits too many cures to the Roentgen ray. While this agent has been helpful in a considerable number of advanced cases, causing a rapid shrinking of the growth and decrease in the amount of fluid, there are as many cases that do not respond at all. He believes that if a patient remains well 5 or more years after the removal of a tumor with subsequent Roentgen ray treatment, the important factor in the cure is not as likely to be the irradiation as the complete removal of a cancer of low malignancy.

Based upon his analysis of 149 cases of primary ovarian cancer, Pemberton¹⁶ is of the opinion that the uterus and both tubes and ovaries should be removed whenever possible, because bilateral growths occur so often and metastases are frequently in the back of the uterus. However, he realizes that it is often difficult and possibly useless to attempt this when the pelvis is filled with the growth and adherent omentum and intestine. The tumor should be removed intact if possible, while tapping, to decrease its size for easier removal, should be

reserved for elderly patients and poor risks. He advises removal of the omentum, regardless whether or not gross metastases can be seen in it, because it is so often affected and may be the source of recurrences later. The peritoneoscope is useful in discovering the extent of the disease. Since such a large percentage (47 %) die within the first 2 years after operation, it might save a patient a useless operation and convalescence if she were not operated upon if the peritoneoscope showed generalized metastases throughout the abdomen. One cannot advocate no treatment, however, because such patients have nothing to lose and operation may prolong life in a few.

At the Massachusetts General Hospital over a period of 33 years only 16 % of the patients with ovarian cancer survived the 5-year period according to Meigs.¹² The results of surgical treatment including the cases that had Roentgen ray therapy, show that in the solid and the solid and cystic group only 9 % of the patients survived 5 years. In the more malignant group of papillary cysts about 23 % survived 5 years. Inasmuch as many of these cysts looked fairly benign, the end results are appalling. There is no doubt that treatment by radiation following surgery is valuable, but although Roentgen ray treatment may slow the growth it does not cure. Roentgen ray treatment should be used in cases that have peritoneal extension, adhesions, whenever cyst fluid has been spilled, when a complete operation has not been done and in all cases in which there is any question as to the perfection of surgery. If a clean and complete excision has been done, radiation should not be used but should be withheld so that it may be used later if necessary. Although it is necessary to treat the entire abdomen, the usual procedure is to treat only two or three fields. This cannot adequately cover the entire abdomen, so that unless each field is marked off and treated, certain areas are sure to be missed. He states that it is the surgeon's duty to make a note of the location of the metastatic areas, where the adhesions were, and where the tumor has extended. These areas should be marked on an abdominal chart and sent to the Roentgen ray department when the patient is to be treated. The surgeon should discuss the lesion with the roentgenologist and decide where and how the tumor should be treated, and it is advisable to have the roentgenologist present at the operation so that he can see the exact location and extent of the tumor. Meigs found that 50 % of the radiation group had solid cancer with 6.2 % living 5 years without disease. This must be contrasted with 12.5 % living in a similar group not radiated. In the malignant papillary cystadenoma group also, the patients not radiated did better than those who were radiated: 24 % as against 18.7 %. It is more hopeful to view the length of life in months of the patients having radiation, as compared to those not having it. In the solid tumors radiation prolonged life, 20.9 months as compared to 7.5 months; but in the cystic group life was slightly longer without it, 21.5 months as compared with 22.9 months. It is apparent from this study that no more people are cured with radiation than without it. It can be stated that cancer of the ovary is a very serious lesion and the solid type rates with the worst of all malignant tumors. If found early, cancer of the ovary is curable, for it is often encapsulated within the ovary and is not serious until the cyst is broken or perforated. Therefore early operation is essential in patients with questionable ovarian

lesions, since it is better to remove a simple cyst or a fibroid because of a mistaken diagnosis than to wait to see whether a given lesion becomes malignant. The preservation of ovarian tissue in women with ovarian cancer of papillary cysts, benign or malignant, is serious, and if this is done in order to allow pregnancy to occur, extreme caution must be exercised in the follow-up to guard against a growth in the other ovary.

A more optimistic note on radiation therapy has been sounded by Jacobs and Stenstrom.⁹ From their experiences at the Cancer Institute of the University of Minnesota they believe that radiation will produce enough cures in carcinoma of the ovary, even when advanced, to make it a decidedly justifiable procedure. The amount of radiation must be adequate and repeated courses are probably advisable. They outline the technique that they have used which has given them a 5-year salvage of about 35%.

Fibroma. It has long been known that fibromas of the ovary are often associated with ascites, but now a new syndrome has been described by Meigs and Cass¹³ in which, in addition to ascites, there is an associated hydrothorax. The importance of such a lesion seems great, for unexplained pleurisy with effusion and unexplained ascites are problems that occasionally confront internists and they should be aware that a benign ovarian tumor may be responsible for these conditions. On the other hand, a gynecologist who finds ascites and hydrothorax in a patient with a pelvic tumor might feel that malignancy was responsible for the conditions. It is important as well as encouraging to know that not only the ascites but also the hydrothorax may be cured by the removal of a benign ovarian fibroma, since such a patient might be doomed as inoperable under ordinary circumstances. The reason for the presence of fluid in the abdomen and chest in these cases is not clear. The ascites has been ascribed for many years to the irritation of the peritoneum by the hard tumor mass. It is possible that such irritation might cause abdominal fluid, but it does not seem possible to explain fluid in the chest by such reasoning. Both fluids seem to be part of the same process, since removal of the ovarian tumor causes both of them to disappear.

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DERMATOLOGY AND SYPHILOLOGY.

UNDER THE CHARGE OF

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THE TRIVALENT ARSENICALS IN SYPHILIS.

SOME RECENT ADVANCES, COMPARISONS AND EVALUATIONS.

Some Theoretical Needs. In reviewing the arseno-therapy of syphilis it is always desirable to keep before one a species of chart of desiderata, and directions along which advance in knowledge and practice is urgently needed.

Stokes and Beerman⁹⁰ have summarized the points on which the clinical tester of drugs and the practising physician tend to query the introducers of the new arsenicals in the treatment of syphilis, as follows: *in the clinical testing:* (a) rapidity of surface spirillicidal action and healing power; (b) evidence of standard or reasonably rapid reversal of serologic tests in early syphilis; (c) a low incidence of relapse, infectious or otherwise; (d) a low incidence of involvement of the nervous system in early syphilis; (e) good effect on resistant syphilitic manifestations, and late syphilis of the important systems; (f) ultimate curative action in man; (g) a low incidence of reaction. *The practitioner desires to know:* (a) whether the drug will injure or alienate his patient by either minor or serious reaction; (b) is its administration so complicated as to constitute an *office* inconvenience; (c) will it cause rapid healing; (d) will it quickly relieve symptoms, especially pain; (e) what will it do for patients with a persistently positive serologic test on the blood. The sales campaigns are drawn primarily on the second group of criteria.

Increased "punch" whether expressed in greater efficacy of smaller doses, fewer injections for a given effect, shortened time for individual or total treatment, greater intensity made possible by lessened toxicity, are the experts' and the public health's first demands. *Lasting or staying power* is the second, and too little emphasized requirement, and one which must be seriously considered in drugs like arsenoxide (Mapharsen), in which a body of conservative opinion believes lack of this quality, real or imagined, to be a disqualification. *Stability and cheapness* are extremely important, since the latter can enormously increase availability, and the former, the spread and safety of handling. In a recent study of state practice, it was observed that the cost of arsenoxide had made impossible its use on a large scale, notwithstanding its obvious desirability in the types of cases under treatment. Stability, both under market conditions and in preparation for use at the hands of inexperienced physicians, has long been a serious shortcoming of neoarsphenamine, particularly troublesome because of its widespread use, and stability is rated a chief recommendation of Mapharsen and arsphenamine. Astonishing difficulties of technique and usability may be bridged or conditioned by this factor.

Simplification of the route of administration should constantly be striven for. Not only should a drug be acceptably and rationally introduced into the body, but questions of the rate of absorption, maintenance of blood and tissue concentration levels, storage and elimination for quick or prolonged effect must be considered. Intravenous therapy is, broadly speaking, an inferior rather than a superior procedure. Nothing more strikingly illustrates an unexpected aspect of such problems than the effect that the drugstore, as the source of the sulfonamides, an effective treatment *per os* of a sort, may have on the control of gonorrhea. Administration by mouth has disadvantages as well as desiderata, among them especially, the lack of control of doses and assurance that the drug is being taken according to schedule.^{25b, c, d, 52, 64, 81} In many particulars intramuscular injection is both theoretically and practically the ideal. No headway has been made in this direction in improving the administration of the trivalent arsenicals in this particular in some time. There is as yet no safe, effective, acceptable intramuscular therapy with the arsphenamines and arsenoxide for adults. Where large bodies of persons must be treated under pressure of time and circumstances, a valuable form of simplification of treatment technique is increased speed. To this Mapharsen^{18, 35, 79} is as important a contribution at the present time as was neoarsphenamine, by the Ravaut concentrated solution technique in the last war.

Precise and unvarying chemical constitution, as demonstrated by crystalline characteristics, which as Tatum⁹⁷ points out, does away with the necessity for constant comparative biologic testing of lots, as in the case of the arsphenamines and uniformity of action dependent on uniformity of constitution, are highly desirable qualities in arsenicals for the treatment of syphilis, and are thus far met only by arsenoxide. Several troublesome groups of reactions, including colloidoclastic changes often held responsible for the nitritoid crisis, and possibly allergic sensitization, may perhaps be controlled or done away with by using arsenicals to meet this requirement.

Further reduction of unfavorable reaction-producing effect on the human subject is unquestionably theoretically desirable, but this has a double-edged quality, because reduction in toxicity has so often seemed among the trivalent arsenicals to parallel reduction in efficiency.^{5, 7b, 56} The differentiation of reactions into incommoding *versus* serious, is important for the public health campaign, for incommoding reaction is as serious in discouraging the control of infectiousness by continuity of treatment, and as much opposed to the calendar regularity of schedule now being emphasized, as serious reaction is losing the individual his chance of cure. Every effort should therefore be devoted both to the devising of preparations which retain therapeutic effectiveness despite diminished toxicity, and equal effort should be devoted to such reasonable and practicable refinement of technique as may do away with or reduce the reactivity attributable to the improper or casual handling of a drug. The importance of stability and speed with safety has been repeatedly emphasized by Stokes,^{87a} who maintains that hurry, which brings out the intrinsic defects of arsenical drugs other than arsenoxide, is basically responsible for the reaction incidence of clinics and individuals day in and day out.

The gradually increasing recognition of the allergen behavior of the

trivalent arsenicals, as illustrated by sensitization effects in arsenical dermatitis, detection of sensitiveness by patch technique, animal experimental work on the induction and prevention of neoarsphenamine sensitization and so forth, indicates that new preparations should be studied in advance for the incidence and if possible avoidance, of idiosyncratic and allergic effects.^{7a, 20a, b, 26, 71, 80, 93, 94} Several of the gravest reactions to the arsenicals, including particularly the so-called hemorrhagic group, have an unpredictability that needs further study along these suggested lines.

The distribution and behavior of the arsenicals in the body still remains a tissue of speculation rather than an orderly array of facts. It may be too much to hope that the "tagged" atom may help us out in this direction; but certainly if the notion is physically entertainable at all, the arsenicals should not be forgotten in the current work based upon the cyclotron. Arsenoxide, particularly because of its crystalline structure, might conceivably be investigated from this standpoint.

Process of Evaluation of Arsenicals. The clinical testing of the arsenicals and thus the determination of the status of new preparations, has long been a weak spot. The tremendous importance of uniformity of performance is at present committed practically entirely to a trypanocidal test which is a useful but essentially foreign laboratory procedure for a spirochetal disease, and to a laborious and extended clinical try-out, the weaknesses of which as well as its value, are demonstrated by such papers as that of Snodgrass,⁸⁵ of Kolmer,⁴⁹ of Moore, Hardy, Robinson and Eagle,⁵⁴ of Harrison,^{39a} of Stokes and Beerman^{7c, 90} and of Cole.¹⁷ The correlation of trypanocidal tests, spirillicidal tests in rabbits, clinical curative effects in rabbits, and the above described complex series of questions governing effect in man, often exhibit serious hitches and disagreements. It deserves repeated emphasis that the behavior of an arsenical in the animal is a guide but not an infallible criterion for its behavior in man. Clinical testing of the relative efficiency of five types of arsenical in the treatment of syphilis were shown not to depend upon a popular method of evaluation—that of the rate of reversal of serologic reactions in early syphilis, by Moore and his coworkers. All five drugs (arsphenamine, neoarsphenamine, silver arsphenamine, Bismarsen, Mapharsen) were shown to reach approximately the same destination in the end with respect to this single criterion.

Cannon and Karelitz¹² demonstrated the difference between three drugs with respect to the time and dosage factors in serologic reversal. Beerman^{7d} has even pointed out the possible effect of bismuth in positively delaying serologic reversal, a finding suggested by the curve of Bismarsen reversal obtained by Moore *et al.* Harrison's paper emphasizing the inconstancy and variability of the rate of disappearance of *Spirochæta pallida* from secretions of early syphilitic lesions following administration of equivalent doses of a variety of batches of neoarsphenamine and arsphenamine as well as sulfarsphenamine and solusalsvarsan, illustrates not only the importance of clinical testing of drugs for uniformity of spirillicidal action in man, but suggests variation in host^{87a} as well as strain of spirochete,^{7b} in addition to the apparently quite clear-cut lot differences among the various manufactured brands. Snodgrass⁸⁵ in reviewing the points for investigation rates a

test of clinical effect on late syphilis as the next objective after a study of toxicity, a point on which Stokes and Beerman⁹⁰ differ with him. The latter maintain that a drug which is not rapidly and effectively spirillicidal in early syphilis should not be released to the medical profession for use in the treatment of syphilis, because of its failure to meet the public health objectives of controlling the spread of the disease. Drugs of slow spirillicidal effect, however, are not useless, inasmuch as they may be of particular value in the treatment of cardiovascular syphilis, in the avoidance of therapeutic paradox, and in the reduction of persistently positive serologic reactions of the blood to negative. Such drugs may also be substituted if ultimately of good effect for reaction-producing spirillicidal drugs employed early in the disease.

Stokes and Beerman discuss, as does Snodgrass, the type of organization, clinical and scientific, which should be charged with the clinical testing of the arsenicals. All these authors emphasize the dangers of the too often commercially exploited general practitioner's report based on a few samples used under uncontrolled clinical and laboratory conditions. The only opinions which should be accepted on the worth of antisyphilitic drugs are those of large well-equipped clinics with competent laboratories working in association with them. In order within such organizations to produce trustworthy work, the clinical investigator must (Stokes and Beerman): 1, subdivide his reports chronologically into periods, and use only identical periods for comparisons, especially of reactions, some of which seem influenced by wave-like "epidemiologic" factors; 2, accept for testing only drugs for which he has the proper clinical material in sufficient amounts; 3, maintain a stable evaluating mechanism, including a laboratory equipped for controlled serologic and darkfield examinations and clinical assistants with not less than 2 years' experience with the disease; 4, have available a follow-up mechanism of not less than 60 % efficiency which will secure continuity of treatment, and return for reexamination over a long period of time; and 5, develop a treatment organization whose performance is constant with reference to the technique of injection, and a normal incidence of unavoidable reaction to ordinary drugs, and which has developed special facility and accuracy in detecting both therapeutic response and reaction to the new drug. It is important to emphasize the time factor in clinical testing which Stokes and Beerman estimate to range from 2 months to 2 decades, depending on the point to be covered.

Laboratory Testing of the Arsenicals. This has until recently been subject to the labor, expense and time consumed by the use of the rabbit and rat as experimental animals, which has virtually necessitated the maintenance of an animal hospital organization in charge of specialists in rabbit syphilis. With the chemical synthetic establishment required the set-up has increased the expense of the manufacture of the arsenicals so that a new drug is almost bogged down by the cost of its introduction before an ampoule is marketed, and the interest of manufacturers is significantly reduced. It is an interesting point in Government regulation of testing and marketing of the arsenical synthetics that the Congressional Act² enabling the Public Health Service to control such products is so worded that only drugs like the arsphenamines can be included under the testing of "biologicals." A drug such as

arsenoxide, now of enormous and extending importance, cannot, because of its molecular constancy and crystalline character, be subjected under the present law to any form of governmental regulation.

The relation as evaluating devices between trypanocidal and spirocheticidal tests for the efficiency of an arsenical has been specially studied again by Probey,⁶⁵ who points out that the minimal effective dose of neoarsphenamine in experimental syphilis may vary from test to test, probably due to the variable factors in the experimental infection, to which the virulence of the organism may contribute, rather than to differences in the curative value of the drugs. He found 17 lots of neoarsphenamine however, representing 7 American brands, to be uniformly active in curing experimental syphilis in rabbits with one treatment late in the active stage of the disease.

The effort to get away from the "animal" type test procedure has led to Eagle's devising a method^{23a,b,c,d,e,f} for the testing of spirocheticidal effect *in vitro*, of which Kolmer and his associates^{46,50} offer a critique. Sanyal,⁷⁵ incidentally, has pointed out the possible usefulness of an electrolytic toxicity test. Eagle tests the spirocheticidal action of graded strengths of the various antisypilitic arsenicals in saline solution. His demonstration of their spirillicidal properties *in vitro* sets aside the long-established dictum that the trivalent arsenicals are relatively non-spirillicidal outside the body. In editorial comment^{25a} on this method the *American Journal of Syphilis, Gonorrhea and the Venereal Diseases* rates Eagle's *in vitro* test as a major contribution to the control of present, and the study of new, arsenicals. Kolmer, Kast, Peterson and Rule,^{46,50} while confirming Eagle's reestablishment of *in vitro* spirocheticidal effect, point out that dilution, duration of exposure, temperature and other important control factors so modify the usefulness of the test, that many of the interpretations offered to date should be reviewed. The method undoubtedly involves complex control factors. Some interesting paradoxes are emphasized by Kolmer *et al.* Mapharsen, for example, was found to be 2 to 4 times more spirocheticidal and trypanocidal than arsphenamine and neoarsphenamine *in vivo*, but, paradoxically, about 5 times less spirocheticidal *in vitro*. Unquestionably this method will bring about some important revisions in technique and interpretation from the laboratory side in the evaluation of the arsenicals.

New (and Old) Drugs. The Drug-of-the-Year (or half-decade) is arsenoxide, whose revival by Tatum⁹⁷ and application to the general therapy of syphilis by his clinical associates, Lorenz and by Foerster^{31,101} and also in mass study by Gruhzit and Dixon,³⁵ is probably the most important single contribution to the arseno-therapy of syphilis since the introduction of neoarsphenamine. The bibliography of arsenoxide (Mapharsen) or as Tatum says, arsenoxide from the arsphenamine, already at this writing includes more than 150 titles. Judged by the short-term elements in the standards of evaluation previously mentioned, arsenoxide (Mapharsen) has met every requirement. It is rapidly spirillicidal, and convincingly effective in the healing of lesions, reduction of serologic tests to negative, and other forms of symptomatic response. For the length of time it has been in use it has an excellent record in the prevention and control of asymptomatic neurosyphilis. The bibliography of the drug is as yet deficient in thoroughgoing study

of infectious relapse. In late syphilis of special systems it is at least as effective as the arsphenamines; in late syphilis of the nervous system, no more and no less effective. Its worth in pregnancy is probably, though not as yet demonstrably, that of the arsphenamines, though Castallo, Coppolino, Rakoff, Roeder and Dickson¹³ in a group of 116 pregnant women, treated with Mapharsen and bismuth, rated the drug definitely less effective than neoarsphenamine in the treatment of syphilis in pregnancy, because it does not afford as good protection to the fetus during the period of treatment and complications in the mother, especially gastro-intestinal, are more frequent than they should be. Morgan,⁵⁵ treating congenital syphilis, rates it more effective in reversing serologic tests than any other arsenical compound previously used. Cornell and Astrachan²¹ gave the drug intramuscularly, and refused to draw conclusions as to its effectiveness on account of the low dosage employed. Howles⁴¹ found this drug good in his experience in treating 204 congenital syphilitics. Chargin and Leifer¹⁵ treated 50 consecutive Wassermann-fast patients with Mapharsen, to find that the drug is neither more nor less effective than any other arsenical in the management of this type of patient. Cole and Palmer,¹³ in a careful study of 242 patients, of whom 185 were in the primary or active secondary stage, employing a total of more than 5000 injections, apparently rate the drug as approximately the equal of the more familiar arsphenamines. There is a notable absence in the literature of comparative series run in similar conditions in the same clinics, using Mapharsen parallel with the older arsenicals.

One of the strongest "talking points" for Mapharsen is the undoubtedly greatly reduced incidence of reaction to this drug. Nitritoid crises, often a serious annoyance with the older arsenicals, is all but absent with Mapharsen. Epstein,²⁶ compiling data from 92,000 Mapharsen injections, found skin reactions, including exfoliative dermatitis, from one-half to one-third or even one-ninth as frequent as with the standard arsenicals. This is especially true of exfoliative dermatitis. Rein and Wise⁶⁹ listed 19 types of reaction recorded to 1939, including practically everything made familiar by the older arsenicals except aplastic anemia, of which at the time of their writing there was not a single recorded case. They report 1 death, but fatal accidents are certainly extremely few.^{48,67,82} One of the strongest tributes to the low toxicity of arsenoxide is the experience of Baehr-Chargin group,³ working with the intravenous drip technique, in which the substitution of Mapharsen in total dosage as high as 1200 mg. has not served to approach the toxicity of neoarsphenamine in an average dosage of 4 gm. (4000 mg.). On the staying power of Mapharsen very little is as yet of necessity available. Raiziss and Severac^{66b} found the toxic and curative dose so close to each other in animal studies that they felt arsenoxide was under a grave handicap. Colonel Harrison (personal communication) has expressed the opinion that the most serious deficiency of Mapharsen will be in the direction of permanence of results. Taking into consideration all the various factors entering into the efficiency of an arsenical, it seems reasonable to expect that as in the case of neoarsphenamine, any existing intrinsic deficiencies will be taken up in the modern systems of treatment by the use of bismuth as a heavy metal,^{39b,88,89,91,96} bringing the level of effectiveness of com-

bined Mapharsen-bismuth therapy fully up to the standards achieved by the conventional arsphenamine and neorsphenamine therapy by combined continuous (CCG) therapeutic systems.

Always more or less parenthetically, but nonetheless usefully, it should be pointed out that Mapharsen is a valuable substitute for other arsenicals, when these have proved reaction-producing in the individual case. Reports on this matter include those of Jordon and Traenkle,⁴⁵ Goldberg,³³ Schoch,⁸⁰ Epstein and Falconer,²⁸ Falconer and Epstein.²⁹

Acetyl-glycarseno-benzene (Solu-salvarsan),^{30,70,74,76-78,100} manufactured in Germany, was submitted to the therapeutic trials committee of the British Medical Research Council in 1933, and reported on by Colonel Harrison in 1939.^{39c} In 1940, Guy, Goldmann, Gannon and Slone³⁷ published an American report of the preparation. This drug has intrinsic theoretical interest because it has apparently no sensitizing properties for animals as distinguished from other arsphenamines, and might therefore conceivably be expected to give rise to fewer idiosyncratic or allergic reactions in man. A concise clinical summary of the two mentioned reports is furnished by the Council on Pharmacy and Chemistry of the American Medical Association.¹⁶ Colonel Harrison and his coworkers found that the drug was not as effective as neorsphenamine; its spirillicidal period in early lesions being as long as 6 days. Instead of being painless, as was hoped, on intramuscular injection, pain was quite frequent, and reactions far from rare, many of them severe, and even fatal. The American authors³⁷ likewise found the reaction incidence to be too high to recommend the drug. Sensitization dermatitides which it was hoped would not develop, and blood dyscrasias likewise appeared in the American series. The drug was therefore given only preliminary status, and not recommended by the Council on Pharmacy and Chemistry.

Thio-arsene (disodium bis-(p-sulfophenyl)(acetamido phenyl)-dithioarsenite), a solution of the mono-ethanolamine salt of sodium p-thiophenyl sulfonate, is added in preparation. Experimental animal results seem to justify its trial in man; Robinson and Moore,⁷² from the Johns Hopkins Hospital, however, report so high an incidence of severe gastro-intestinal reaction as to necessitate marked reduction in the advised dose. The reactions are so severe, that patients refuse to continue treatment with the drug. It cannot be used in patients who have had a dermatitis from the previous use of the arsphenamines. It compares unfavorably with the arsphenamines, and with bismuth in its effect on surface spirochetes, on the healing of lesions, and on the blood Wassermann reaction. Becker and Obermayer⁴ reported on the use of the drug simultaneously with bismuth but since the series was uncontrolled by a group treated by bismuth alone, conclusions are unsatisfactory. The drug should therefore not be recommended for use at the present time.^{19,24}

Trisodarsen (trisodium salt of 3,3' diamino 4,4' dihydroxyarsenobenzene N,N' dimethylene sulfonic acid) has had quite an extended and carefully conducted clinical trial at the hands of the Syphilis Clinic of the University of Pennsylvania and of Givan and Villa³² in the Pediatrics Department of the Long Island College of Medicine, and the Brooklyn Eye and Ear Hospital. The former authors found the reac-

tion incidence compared with several other series, including arsphenamine, neoarsphenamine and Mapharsen, to compare favorably with and even to be lower with respect to mild reactions than that of most of the named drugs. With respect to severe reactions, there was some tendency to increased frequency of dermatitis and hemorrhagic reaction, as previously observed in most of the sulfarsphenamine group of drugs. The distinctive characteristics of Trisodarsen include superiority to neoarsphenamine with regard to the rate of healing of primary and secondary lesions; and effect on the serologic reactions of the blood, intermediate between neoarsphenamine and arsphenamine; an exceptionally low incidence of asymptomatic neurosyphilis as evidenced by spinal fluid examination. In subsequent investigations covering a period of 8 years, this position has been reasonably well maintained. It would appear that the superior clinical effectiveness of the drug must be measured against an undoubted tendency to dermatitic and hemorrhagic reaction, which is relatively rare with Mapharsen for example. Givan and Villa, employing Trisodarsen in congenital syphilis, reported it well tolerated by the intravenous and intramuscular routes, and particularly free from paravenous infiltration when the drug was delivered outside of a vein. Gastro-intestinal reactions are more numerous than the average, but are attributed by these observers to fright on the part of the children. The drug can be substituted in patients having reactions to neoarsphenamine. It was markedly effective in the treatment of interstitial keratitis, and an unusually high reversal of positive Wassermann reaction (76%) was secured by the use of the drug alone or in combination with other drugs. The tonic effect was notable.

Bismarsen (bismuth arsphenamine sulfonate), on the market 14 years, has been reported since 1931 by many authors.^{6,14,36,38,51,57,66a,68,90,92,95,98} The substance of these evaluations is that Bismarsen has an established field of usefulness, and is at its best in the treatment of children and in cardiovascular syphilis. It cannot be given intravenously, but is of material usefulness where the intramuscular route is the only one available. The long series of relatively frequent injections (twice weekly) necessary to the best results in early syphilis are a handicap to its use in this phase of the disease, and it has demonstrated no superiorities in the treatment of latent and late syphilis other than cardiovascular. The reaction incidence is low, but as in the case of Trisodarsen, exhibits a tendency towards hematopoietic accidents, which seem to accompany the sulfarsphenamine group of drugs. Such reactions are, however, rare.

Sulfarsphenamine exhibits the curious paradox of warm allegiance on the part of some undoubtedly competent observers, side by side with damnation from others equally competent. This drug relatively non-reaction-producing and therapeutically effective when given to children, has been subjected to so much criticism on the score of grave reaction produced in adults (hemorrhagic and hematopoietic injury and dermatitis) that its status was reviewed by the Council on Pharmacy and Chemistry in 1932^{1a} and the *pros* and *cons* there discussed. The late Dr. Albert Pfeiffer⁶² who strongly supported its continued general use by the New York State Department of Health compared the reaction incidence in 29,510 reactions with the statistics of the Coöperative

Clinical Group, insisting that sulfarsphenamine's record was fully equal to that of the other arsphenamines. He stated that in the New York State Clinics, there were no cases of aplastic anemia, cerebral hemorrhage, acute yellow atrophy or ocular damage, and no deaths from the drug. Osborne, Rickloff and Butler⁵⁸ in parallel tables showed that the incidence of jaundice was 1 in 800 injections for arsphenamine (606); for sulfarsphenamine 1 in 179 injections. Dermatitis occurred in 1 of 859 injections following arsphenamine, whereas it occurred in 1 of 298 injections following sulfarsphenamine. There were no cases of purpura following arsphenamine, whereas 2 followed sulfarsphenamine. The United States Navy Medical Department,⁸⁶ using sulfarsphenamine from 1925 to 1939, among 29,438 injections, reported 17 mild, 8 severe and no fatal reactions to sulfarsphenamine. During the year 1939, 943 doses of this drug were administered with no reactions whatsoever. In the 15-year period the incidence of reactions of 1 to 1178 doses of sulfarsphenamine is somewhat higher than the average ratio of 1 to 1470 doses of 8 arsenicals, trivalent and pentavalent. In general, it is clear therefore that the weight of opinion is opposed to the use of this drug in adults, but sanctions its use in the treatment of children.

Silver arsphenamine continues to be used with accumulating evidence that it is really from the therapeutic standpoint one of the most effective of the arsphenamines. Cannon,^{11a} in comparing it with arsphenamine and neoarsphenamine, found serologic tests reversed in a fewer number of injections of silver arsphenamine, a smaller amount of the drug, and a slightly shorter length of time than the neoarsphenamine. Its superiority over neoarsphenamine was apparent also in the healing of lesions, and in the achieving of "satisfactory" end-results it stood only very slightly below neoarsphenamine. The fear of argyria which has had an important influence on the use of this drug is well grounded. Pillsbury and Hill⁶³ collected 19 cases of argyria from the use of silver arsphenamine. In their summary it stands third among all silver compounds responsible for argyria. While this incidence is not intrinsically high in proportion to the use of the drug, the complications are so disconcerting and medicolegally serious as materially to discourage the use of the drug.

The comparative values of arsphenamine (606) and neoarsphenamine (914) have been so many times reviewed that only a brief summary seems necessary. All syphilologists of experience concede to "AB" (arsphenamine 606) the premier place among all arsenicals for the treatment of syphilis (other than paresis). Cannon^{11b} who has especially carefully studied this question and consistently maintained the superiority of 606, and who has devised a syringe technique for its use, seems to have established the position of the drug beyond peradventure. There is much evidence that the toxicity of 606 is steadily on the decrease, probably due to improved methods of manufacture, and that it is now probably the least toxic of all the arsphenamines. Whether Cannon's^{11c} simplified technique which employs large syringes, can achieve enough popularity to reintroduce the drug to practice, remains to be seen. Neoarsphenamine is now the most reaction-producing of the standard and generally accepted arsenicals in the treatment of syphilis. Its therapeutic worth has been reinforced by bismuth so that the modern systems in which it is employed are as effective as

those employing 606. Whether or not Mapharsen with its lower reaction incidence and quicker and simpler administration can displace it altogether from practice should, and perhaps will, depend on the demonstration for arsenoxide, of an equal ultimate effectiveness in cure. No changes have been made in the physical and chemical characteristics of marketed neoarsphenamine which justify any change in the established technical features of its administration, namely, no agitation or aëration on mixing, and extremely slow injection. Apparently the work of Probey⁶⁵ indicates that much of the lack of uniformity and therapeutic efficiency of various lots of neoarsphenamine among American manufacturers at least has been ironed out.

New Techniques in the Use of the Arsenicals. The previous discussion has indicated that neoarsphenamine has now an established place in the standard therapeutic system for the treatment of syphilis, including those of the United States Public Health Service and Coöperative Clinical Group ("30-60-03" and "24-60-100 plus"),^{87b} and in the British-Scandinavian intermittent system published parallel with the American Continuous in the League of Nations Special Commission report. There is therefore no longer anything to be gained by the criticism of the practitioner who uses neoarsphenamine as the easier of the two available drugs for, as has been indicated, bismuth has apparently taken up the shortcomings of the weaker arsenical, and produced an ultimate result essentially equal to that attained by the use of 606. Attention should be directed therefore to other matters, such as the disappearance of the differential in dosage between male and female, both being treated essentially alike; the optimum arsphenamine and neoarsphenamine dosage based on weight; the superiority in ultimate results of large over small doses; and the tendency to use longer series of injections with neoarsphenamine and Mapharsen than with 606. The continuity of treatment during the arsenical phase in the treatment of early syphilis is repeatedly emphasized by all American studies as demonstrably superior to any form of intermittence practised in this country. As yet no satisfactory studies have been made of the reason for the conspicuous rapidity of reversal of serologic tests which occurs in early syphilis under the arsenical alone, particularly in the case of 606, and the lag which follows the employment of a heavy metal, especially bismuth. That there is a considerable range of intensity possible in what has ultimately been shown to be effective treatment of syphilis with the arsenicals is apparent from Padget's⁶¹ recently published study of the treatment of early syphilis and from the description of the intensive system of treating the transient syphilitic at the United States Public Health Service center at Hot Springs, Arkansas. As described by Waugh and Milovich⁹⁹ in a discussion of severe reactions to arsphenamine, the "doubled-up" initial course compares with the old Southard and Solomon system for the treatment of paresis minus the doubling of the standard dose. The incidence of severe reactions under such a régime is somewhat higher than under the generally accepted figures of the Coöperative Clinical Group, for a less intensive type of treatment (2.44 severe reactions per 1000 arsenical injections, as compared with 1.99). The increase in frequency of reaction, however, can hardly be described as proportionate to the increase in intensity. At the Hot Springs Clinic the incidence of icterus was 84 % higher

and crustaceous dermatitis 10% lower under the intensive system than under the standard relatively milder systems of the Coöperative Clinical Group.

Intensification has, of course, reached its peak in the universally interest arousing so-called 5-day treatment system for early syphilis which has been continuously studied by the Baehr-Chargin group³ in New York. It is, of course, impossible to offer a final evaluation of such a technique at this stage of its use. The unfortunate consequence of a premature popular excitement and demand has been visited upon this system of treatment, notwithstanding reasonable caution in reporting it to the medical public. The original publications by Hyman, Chargin and their associates^{16,40,42a,b,43} was followed by another report by Hyman, Chargin and Leifer in 1939,⁴⁴ which led apparently to the placing of the investigation in the hands of a committee headed by the Surgeon-General of the United States Public Health Service and the Commissioner of Health of New York City. The report of the members of this committee at a conference called by the Commissioner of Health on April 12, 1940, is a succinct, carefully prepared and excellently controlled statement of technique, complications, reactions, and clinical results to date. In the discussion of the method which followed, general recognition was given to the importance of the drip or continuous method of administering a parasitocidal drug as a significant clinical advance. It was indicated, however, by the discussion that the work conducted to date was insufficiently supported by laboratory studies on animals, particularly with reference to toxicologic effect. It was clear that the reactions induced by the treatment chiefly preoccupied the commentators, and Moore in discussion was particularly vigorous in directing attention to the high incidence of hemorrhagic encephalitis whose frequency, 1 to 100 in the 5-day series, compared very unfavorably with perhaps an incidence of 1 to 15,000 under the standard treatment systems. Generally speaking, the reports failed to demonstrate within the limitations of time and observation any striking superiority in aggregate cures and absence of relapse over the standard systems of longer duration such as those of the Coöperative Clinical Group. The materially greater safety of Mapharsen employed in the 5-day system's second series and the possibility of developing modifications of the system in the form of repeated injections during each 24-hour period without the necessity for continuous intravenous drip have also received attention. It is generally agreed that the method is one for specialists under the most rigidly controlled conditions, and is not to be commended in the present state of knowledge to the practising physician or for general use. So far as can be judged from the available publications, the chief merit of the method is that of time-saving rather than safety or superiority of ultimate results. Whether or not time-saving in itself justifies the greater assumption of risk, or is even a desideratum in and of itself, is a proper matter for future evaluation.

The report of the Council on Pharmacy and Chemistry in the *Journal of the American Medical Association* in 1940^{25e,f} seems generally to be in accord with this estimate.

Non-specific Uses of the Arsenicals and Combinations of Their Use With Non-specific Measures. It is too easily forgotten in the emphasis on arsenicals as specifics, that a considerable portion of their effect is

probably not directly upon the *Spirochæta pallida* and that they are significantly useful in other conditions than syphilis. The outstanding evidence of this, of course, is the action of tryparsamide, a practically non-spirillicidal pentavalent arsenical, upon a highly specific manifestation of neurosyphilis, namely, general paresis. Several recent publications deal with the non-specific effects of the arsenicals in conditions other than syphilis. Duehr, Weissmiller, McIntosh, Cooper and Tatum²² have directed attention to arsenoxide (Mapharsen) as a therapeutic agent for *Vincent's infection*. Apparently it is at least as effective as neoarsphenamine when used locally and the authors claim for it quicker and more satisfactory results than those obtained by any other agents. The technique, as illustrated by 1 of their cases, consists in the use of Mapharsen mouthwashes or a swab of a 1% solution of the drug with a gargle of 0.4% of the drug and the intravenous injection of 30 mg. of Mapharsen for the initial dose and three successive intravenous injections of 60 mg. each at 4-day intervals. An alkaline gargle is recommended to clear the mucosæ of secretions before the Mapharsen mouthwash is employed. Young and McLendon¹⁰² report on the treatment of *induced malaria* in negro paretics with Mapharsen and tryparsamide. It has apparently been claimed that quartan malaria responds in these patients as satisfactorily to Mapharsen and bismuth as to quinine. Goldman³⁴ is quoted even as rating Mapharsen as immeasurably more effective than quinine in quartan infections, and notably more effective than arsphenamine and neoarsphenamine. He employed arsenoxide for the termination of tertian malaria in place of quinine. Young and McLendon¹⁰² took pains to control their use of arsenoxide and tryparsamide for the termination of quartan malaria by reëxamination of blood smears as long as 22 weeks after the completion of the Mapharsen course, and found all of their patients to have become asymptomatic malarial carriers. Three of their quartan malaria patients who received tryparsamide examined 1 year after the completion of tryparsamide treatment still showed *P. malariae* in the blood stream. The use of the arsenicals for the purpose of terminating malaria unaided by quinine would therefore seem unwise.

Rosebury, Foley and Rights⁷³ report on the effect of neoarsphenamine and sulfarsphenamine in *experimental fusospirochætal infection* in guinea-pigs with almost uniformly disappointing results. Both neoarsphenamine and sulfarsphenamine were ineffective when administered systemically and only ameliorative when administered intralocally into the center of the lesion. Of the two neoarsphenamine was the more effective. Osgood, Brownlee and Joski^{59,60} studied the relative effectiveness of neoarsphenamine, Mapharsen, sulfanilamide, sulapyridine, sulfathiazole, and sulfamethylthiazole on infections with *Strep. viridans* in bone marrow cultures. Neoarsphenamine in concentrations of 1 to 150,000 was effective against more strains than any of the other drugs tested, but was less effective than sulfathiazole or sulapyridine against certain strains. In a concentration of 1 to 1,500,000 it is effective against certain strains, but not as uniformly effective as neoarsphenamine in concentrations of 1 to 150,000.

Buchtel and Cook,¹⁰ from the Mayo Clinic, employed neoarsphenamine in treatment of *infections of the urinary tract* in a total of 250 cases, with marked success, in pyelonephritis of coccal origin but not in bacil-

lary pyelonephritis. The drug fails in the presence of stones, marked obstructions, severe focal infection, infection referable to *Strep. fecalis*, non-specific prostatitis, and chronic cicatricial pyelonephritis. Acidification of the urine improves the result. Small doses, interestingly enough, are as efficacious as the larger ones, and improvement will occur after the first or second injection, if it occurs at all.

The use of the *arsenicals in conjunction with fever therapy* is probably more general and developing more rapidly than the available literature indicates. Simpson was among the earlier enthusiasts in recommending the simultaneous use of antisyphilitic drugs (Bismarsen or neoarsphenamine and bismuth) and fever therapy in early syphilis.^{83,84} Kemp⁴⁷ pioneered in the simultaneous use of tryparsamide and hyperpyrexia in the treatment of paresis. Epstein²⁷ reported a series of 87 patients with central nervous system syphilis who were treated with fever therapy produced by the blanket method and with drug therapy consisting of tryparsamide and bismuth salicylate, or occasionally, neoarsphenamine simultaneously. This combined use of chemotherapy and artificial fever therapy gave excellent results. Bennett and Lewis^{8,9} reported on 72 cases of asymptomatic and clinical neurosyphilis treated by combined artificial fever and chemotherapy. Of 10 of their cases strongly positive cerebrospinal fluid findings were reported as completely reversed to negative in 7, and partially reversed in 2, by the combination. In 19 patients with paralytic dementia, treated by the combined method, complete remission with full occupational recovery followed in 14, moderate improvement in 3, and no improvement in 2. In 31 cases of tabes dorsalis of the most severe type, complete relief of all predominating symptoms occurred in 52%, improvement in 35%, and only 4 failed of improvement. Gastric crisis was completely or partially relieved in 11 out of 15 cases. In severe disabling types of meningovascular neurosyphilis, 10 obtained complete relief of predominating symptoms out of 12 treated. Fever was induced by the Kettering hypertherm and Mapharsen or Bismarsen employed as the arsenical. Menagh⁵³ employed in 130 patients neoarsphenamine in 0.6-gm. to 0.9-gm. doses, beginning with the second bout of fever, and administered in 41 cases with the patient's temperature at 105° F. The drug was well tolerated, and Menagh believes therapeutic efficiency was markedly increased.

It is proposed to prepare a more extended discussion of reactions to the arsenicals as the next contribution to this review.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF FEBRUARY 18, 1941

The Collection and Analysis of Fluid From Single Glomeruli and Tubules of the Mammalian Kidney. A. M. WALKER, JEAN OLIVER and P. A. BOTT (Department of Pharmacology, University of Pennsylvania, and Department of Pathology, Long Island College of Medicine). In anesthetized rats, guinea pigs and opossums a technique has been developed for rendering the kidney accessible to direct puncture of its nephrons in a manner similar to that which was found serviceable in studies of the amphibian kidney. At a preliminary operation a unilateral nephrectomy was performed to allow compensatory hypertrophy of the remaining kidney to occur. The surface of this remaining (left) kidney was protected from exposure by a layer of warm oil and illuminated by light transmitted through a lucite rod. Punctures of tubules and, in a few cases, of glomeruli was accomplished by quartz pipettes and fluid was collected in amounts sufficient for ultramicroanalysis (0.1 to 1 c.mm.). After marking the punctured nephron by the injection of ink for subsequent identification, the kidney was fixed in formalin, macerated, and the nephron isolated by microdissection in its entirety. By means of stereoscopic photographs and camera lucida

drawings, accurate measurement of the various segments were then made which exactly identified the site of puncture.

Sixty successful experiments have been performed. The results show that gomerular fluid is free from detectible amounts of protein, has the same vapor pressure as blood plasma and contains reducing substances and exogenous creatinine in the same concentration as occur in plasma water. Glucose is reabsorbed by the proximal tubule in these animals as in amphibia. The increasing concentrations of creatinine and glucose (after phlorhizin) in tubule fluid indicate that the proximal segment reabsorbs about 80% of the fluid in glomerular filtrate; this fluid reabsorption is accomplished without any increase in vapor pressure of the tubule contents. The tubule fluid/plasma concentration ratio of chloride reaches 1.5 early in the proximal tubule; this finding, in view of the vapor pressure observations and of preliminary sodium analyses, implies the preferential reabsorption of another anion (—HCO_3 ?) by the proximal segment.

Correlation Between the Secretory Power of the Frog Kidney and the Molecular Configuration of Organic Compounds. RUDOLF HÖBER (Department of Physiology, School of Medicine, University of Pennsylvania). In previous experiments on the isolated Ringer perfused frog kidney, it has been found that the sulphonic acid azo dyestuffs undergo secretory transfer across the proximal tubules, provided the sulphonate groups are attached to one of the molecular halves of these dyes, whereas the distribution of the sulphonate groups to both halves, in general, impedes the secretion. It was concluded that a polar-non-polar or a hydrophilic-organophilic structure is a prerequisite for the attachment of the dye molecule to the surface of the kidney cells. These previous studies have been extended with the use of more simple organic compounds. The kidney was supplied with only one-half of the azo dye molecules and this half, upon reappearing in the secretion, was coupled in a diazo reaction to the other half and determined colorimetrically. The following results were obtained: the monosulphonates of naphthylamine, naphthol and aminonaphthol, irrespective of the mutual location of the NH_2 , OH and HSO_3 groups, appear in the secretion at a higher concentration level than that in the perfusion fluid, whereas the disulphonates fail to become accumulated. It is suggestive to interpret these results in a way similar to that proposed with regard to the behavior of the azo dyestuffs: organotropic affinities are exhibited by the naphthalene ring system as well as by the NH_2 and OH groups, hydrotropic affinities are exhibited by the sulphonates. If the opposing forces balance each other, there is an attachment of the molecule at the interfacial boundary, a preliminary step in the active transfer. This hypothesis is supported, for instance, by comparing: 1, aminonaphthalenesulphonic acid; 2, sulphanilic acid; 3, sulphanilyl-sulphanilic acid; 4, sulphanilyl-sulphanilamide; 1 and 3 were concentrated in the secretion, 2 and 4 were not.

Application of the Heart Rate Recorder to Pharmacological Research. KLAUS UNNA and MICHAEL KNIAZUK (Merck Institute for Therapeutic Research). A method has been demonstrated which permits the continuous recording of the heart rate on an ordinary smoked paper kymo-

graph simultaneously with other recordings in experiments on anesthetized animals. The method is based on amplifying the heart potentials and feeding the amplified impulses to a mechanical counter. The heart potentials are picked up by electrodes from the mouth and the rectum of the animal and amplified by a portable A.C. operated amplifier. The amplified impulses are counted by a mechanical counter which consists of two electromagnetic step motors that alternate automatically, each counting for a period of 10 seconds. The total number of impulses received during this interval is recorded on the kymograph by a writing point connected to the counter by a cable. The number of impulses is recorded as a proportional linear displacement. A difference of one impulse per 10 seconds is clearly visible. The counter is adapted to record frequencies up to 400 per minute.

Experiments have been presented demonstrating the effect of adrenalin, atropine, carbamylcholine and digitoxine on the heart rate as measured and recorded by this method.

Isolation and Properties of a Pigmented Complex Macromolecular Material From *Streptococcus Pyogenes*. M. G. SEVAG, J. SMOLENS, and KURT G. STERN (Department of Bacteriology, University of Pennsylvania, School of Medicine, and the Laboratories of Physiological Chemistry, Yale University, School of Medicine). A pigmented complex macromolecular material has been isolated by ultracentrifugal methods from *Strep. pyogenes* disintegrated by sonic vibration. The size and complexity of this substance are comparable to some of the viruses isolated from animal sources. This material, in solution, is dark green, opalescent in reflected light and clear in transmitted light. Its chemical analysis is: 9% to 10% total nitrogen, 0.8% to 1% phosphorus, 0.75% to 0.82% purine nitrogen, and 10% to 17.2% lipid. The presence of purine nitrogen, phosphorus, and the positive orcinol test show that it contains nucleoprotein. The nucleic acid has been characterized as a d-ribose type. Serologic data show that this material also contains a group-specific carbohydrate. In addition to these constituents a green pigment is present. The pigment has not as yet been characterized. Tests for Fe, Mg, Ni, and Cu are negative. The density of the macromolecular substance is 1.22, and its specific partial volume 0.816. By means of the analytical ultracentrifuge the sedimentation constants are found to range from 110 —to 548×10^{-13} cm/sec/dyne for 8 determinations. The average calculated diameter is 42 millimicrons. The method of preparation and the presence of molecules of varying but overlapping sizes appear to be responsible for the variation of the sedimentation constant.

Measurement of Sensitivity of the Smallest Blood Vessels in Human Skin to Graded Mechanical Stimulation. S. R. M. REYNOLDS (Department of Physiology, Long Island College of Medicine). The immediate object of this study was to devise a simple procedure by which it would be possible to measure the sensitivity of the smallest blood-vessels in human skin. This was desired in order that comparison might be made of the sensitivity of the blood-vessels in different individuals and in the same individual from time to time. No present method appeared to do this. Of the known physiologic responses of

the smallest vessels, those to mechanical stimulation seemed to lend themselves most suitably to the purpose. It is well known that a light but adequate stroke will elicit a transient area of paleness of the skin resulting from constriction of the capillaries; that a heavier stroke will give rise to a strong, continuous red line of vasodilatation against a surrounding background of constriction. A device was constructed whereby it was possible so to regulate the force (weight) applied and the speed of its application over a given region (from which duration of the stimulus was determined) that a response intermediate between those described above could be obtained. This threshold response consists of an area of vasoconstriction in the center of which is a just, but easily discernible beginning red reaction. It is possible to read the reaction to within less than $\pm 10\%$ of the weight applied. It is found that a typical strength-duration curve is obtainable; that it represents threshold responses throughout; that it is quite constant, from day to day, for a given individual. The effects of certain experimental procedures were determined. These include the effects of complete circulatory stasis, partial venous occlusion, systemic anoxemia and hypercapnea, and elevation of the skin temperature. Following the suggestion of Lassalle, an index of the excitability for the several curves was determined. By the use of this, the relative sensitivities of the blood-vessels of different individuals is made. A normal average value from which statistically significant values may be appraised remains to be determined. When this is done, it should be possible to study sex, age, seasonal, climatic, pharmacologic, pathologic and other influences upon the sensitivity of the smallest blood-vessels of the human skin.

ERRATUM.

In the article by Reinhold, Flippin, Schwartz, and Domm in the January 1941 issue a comma should be added after "100 cc." on page 107, line 3, so as to read: "Because of the low solubility of the drug in water, about 10 mg. per 100 cc., solutions for standards were prepared by addition of approximately 0.4 cc. of normal sodium hydroxide solution to 100 mg. of sulfapyrimidine crystals."

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

MAY, 1941

ORIGINAL ARTICLES.

OBSERVATIONS ON THE PATHOLOGIC PHYSIOLOGY OF THE
INSULAR AND EXTERNAL SECRETORY FUNCTIONS
OF THE HUMAN PANCREAS.

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THIS report includes observations on three series of patients and illustrates the effect of abnormal conditions of the pancreas on its external and internal secretory functions. The first group includes cases of hyperinsulinism due to tumor of the islands of Langerhans; the second consists of 3 cases of hyperinsulinism that had three-quarters of the pancreas removed, and the third group, 3 patients that had the head of the pancreas removed for carcinoma.

I. We believe that it is of interest to tabulate the glucose tolerance figures in our relatively large series of cases of hyperinsulinism before and after removal of histologically verified tumors of the islands of Langerhans and to plot curves of their mean values (Table 1 and Charts 1 and 2).

While the charts vary considerably, there is a decided trend towards a diabetic curve. In some cases this tendency is present 1 year after the tumor has been removed. The cause is purely conjectural at the present time. However, one may assume that overproduction of insulin by the tumor depresses its formation by the remainder of the islands, resulting in a relative insufficiency of insulin. Due to the increased oxidation of glucose, disturbances in glycogen storage may also be a factor. The Conns⁴ speak of a

fasting blood sugar level of 310 mg. per 100 cc. several weeks after the removal of an adenoma causing hyperinsulinism.

A somewhat analogous reaction is observed clinically in cases of hypothyroidism. If one withholds thyroxin after it has been given in sufficient quantity to restore normal metabolism, the basal metabolic rate may decrease to a point considerably below what it was at the outset.

The average minimum blood sugar in this series was 38. It is obvious that the glucose tolerance test is not as decisive in the diagnosis of hyperinsulinism as is the constant occurrence of low fasting blood sugars, associated with loss of consciousness or other severe nervous derangement and the prompt recovery on the exhibition of sugar.

II. In 3 cases of hyperinsulinism in which no tumor was found at operation, three-quarters of the pancreas was resected in order to decrease the supply of insulin. This, however, was ineffectual. At a subsequent operation the duodenum was mobilized and the adenoma was found and removed.

Case Notes. CASE 1.—Z. G. No. 512939. Age 45. At the second operation the pancreatic remains measured 4 by 3 by 2 cm. The dextrose tolerance test was as follows:

BLOOD SUGARS AFTER INGESTION OF DEXTROSE.

Fasting.	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.	Time after removal of adenoma.
108	141	163	137	..	10 days
95	167	142	3 months
90	166	178	133	127	30 months

Her fasting blood sugars since have varied between 81 and 113 and she has had no symptoms of insulin shock or diabetes.

CASE 2.—I. M. No. 530663. Age 22. Similar to Case 1. Dextrose tolerance test after removal of the adenoma was as follows:

BLOOD SUGARS AFTER INGESTION OF DEXTROSE.

Fasting.	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.	Time after removal of adenoma.
119	153	153	152	149	18 days
103	127	109	..	28 months

CASE 3.—E. S. No. 475076. Age 30. Similar to the foregoing cases in all respects. The dextrose tolerance test after operation was as follows:

BLOOD SUGARS AFTER INGESTION OF DEXTROSE.

Fasting.	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.	Time after removal of adenoma.
122	237	282	233	288	2 weeks
110	190	278	200	6 weeks

In this group after operation the same tendency to delayed removal of glucose from the blood is manifest, but it is remarkable that after a time (about 2 years or sooner) glucose utilization

TABLE 1.—BLOOD SUGARS AFTER INGESTION OF 100 GRAMS OF DEXTROSE BY MOUTH IN 17 CASES OF TUMOR OF THE ISLANDS OF LANGERHANS.

Hist. No.	Time of test.	Fasting.	½ hour.	1 hour.	2 hour.	3 hour.	Remarks.
540606	Before operation	26*					
	Before operation	35	93	91	142	94	
	Before operation	35	103	147	163	141	
	Before operation	40	..	166	200	100	
554410	Before operation	33*	At operation adenoma together with tail and part of body of pancreas removed.
	Before operation	71	143	154	170		
	Before operation	55	148	167	127		
	15 days after operation	95	174	229	234	90	
	75 days after operation	89	118	117	81	75	
	9 mos. after operation	88	165	190	170	104	
592078	Before operation	40*					
	Before operation	40	147	110	131		
	30 days after operation	129	181	220	209		
	11 mos. after operation	102	185	200	181	80	
389424	Before operation	30*					
	Before operation	30	34	101	147		
	Before operation	35	132	135	119		
	9 days after operation	100	145	..	230		
	16 days after operation	91	180	176	130		
530663	Before operation	27*					
	Before operation	64	..	86	115		
350794	Before operation	47*					
	Before operation	58	104	130	119		
	8 mos. after operation	87	111	133	95	70	
475076	Before operation	20*					
	Before operation	33	176	188	197		
512939	Before operation	30*					
	Before operation	85	154	235	246		
546637	Before operation	37*					
	Before operation	48	108	96	246	203	
	Before operation	36	110	85	156		
	Before operation	46	91	97	158	165	
	18 days after operation	106	..	160	189	150	
434383	Before operation	30*					Part of body and tail of pancreas removed with tumor.
	Before operation	64	108	..	133	..	
	16 days after operation	90	..	207	207		
	14 mos. after operation	97	253	212	163		
306695	Before operation	38*					
	22 days after operation	61	164	171			
583382	Before operation	33*					
	Before operation	42					
	11 days after operation	105	170	..	115		
563920	Before operation	45*					
	Before operation	74	180	258	252	170	
	Before operation	45	89	92	90		
510933	Before operation	54*					
	Before operation	60	95	167	182	103	
	Before operation	60	133	153	133	173	
	Before operation	59	132	232	194	168	
428308	Before operation	57*					
	Before operation	57	102	78	65	68	
421465	Before operation	43*					
	Before operation	52	130	105	162		
605580	Before operation	35*					
	Before operation	64	98	125	122	83	

* Minimum.

assumes the normal rate in spite of the absence of three-quarters of the pancreas. Obviously, the human pancreas, like the kidneys and the liver, has an enormous functional reserve.

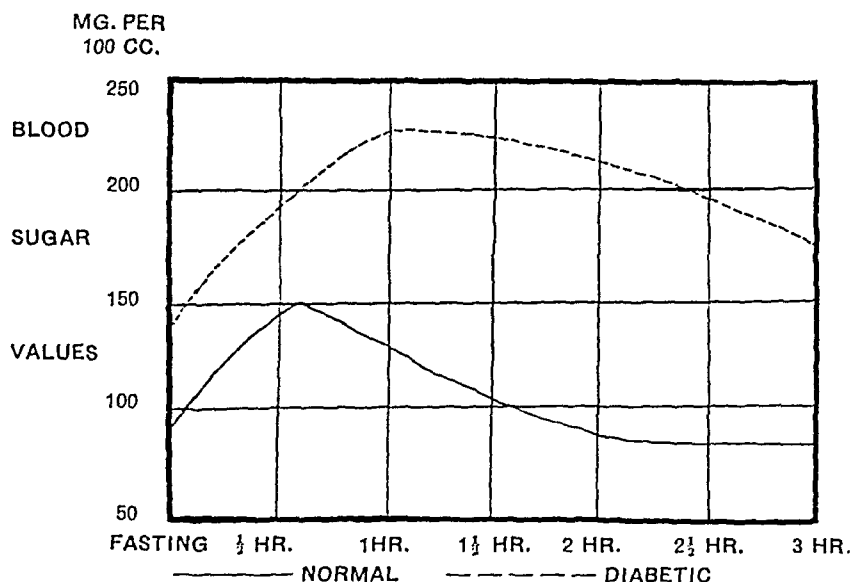


CHART 1.—Diabetic and normal blood sugar assimilation curves after 100 gm. of glucose by mouth.

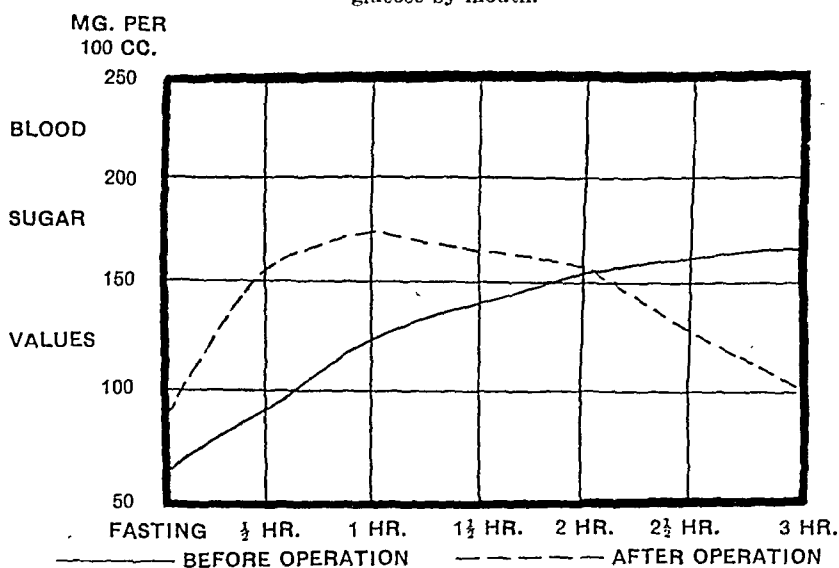


CHART 2.—Mean glucose assimilation curves after 100 gm. of glucose by mouth in 17 cases of hyperinsulinism due to tumors of the islands of Langerhans.

III. The absence of pancreatic juice in the intestine of dogs leads to wide variations in fat absorption⁵ that are unexplained at the present time. The stomach and small intestine secrete weakly active lipases and it is conceivable that a compensatory increase in

their activity occurs when pancreas lipase is unavailable. The bile also contains a weak lipase. However, Koskowski and Ivy's work on depancreatized dogs with fistulae of the small intestine⁸ does not support this idea. In dogs with isolated intestinal loops (Thiry-Vella fistula) Jansen⁷ demonstrated a weak lipase active at about the neutral point.

Ralli *et al.*⁹ observed that 3 normal dogs absorbed 97% and 95% of ingested fat and protein; but after ligation of their pancreatic ducts, fat absorption was reduced to 71%, 71% and 47% and protein absorption to 73%, 72% and 33% respectively. Selle and Moody¹¹ found an average fat absorption of 75% in 4 pancreatectomized dogs. This was unimproved by the administration of dried

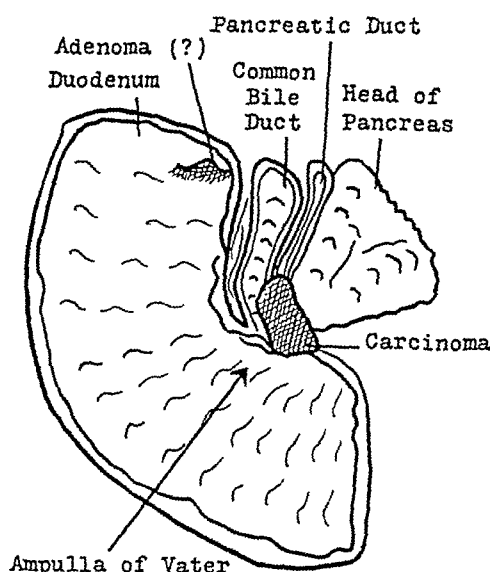


FIG. 1.—Carcinoma of the ampulla of Vater.

pancreas. In 7 dogs deprived of pancreatic secretion, Schmidt *et al.*¹⁰ noted a 60% improvement in fat and protein absorption after feeding dried pancreas. They gave as much as 25 gm. of the dry powder to dogs weighing from 11 to 14 kilos.

In the human, clinicians have attached considerable importance to the activity of the pancreas in the digestion and absorption of fats.

One author states that the absence of pancreatic secretion from the intestine results in bulky, soft, light-colored and highly fatty stools.⁶ Another source, however, says that "there is evidence to show that a substitute for pancreatic juice may, if necessary, be manufactured by other digestive glands in the duodenum, especially Brunner's glands. Thus, the suppression of the pancreatic juice may result in only temporary difficulties. The development of frequent fatty, gray stools is supposed to be due to interference with normal secretion and is called pancreatogenous diarrhea."³ A third

TABLE 2.—CASE 1.

M. J. Age 49. History 440080.

Diagnosis: Carcinoma of ampulla of Vater.

First operation: January 25, 1935. Gastro-enterostomy.

Cholecystgastrostomy.

Ligation of common bile duct.

Second operation: February 7, 1935. Removal of duodenum and part of pancreas.

Death: Metastatic carcinoma. April, 1937.

DAILY FAT ABSORPTION IN THE ABSENCE OF PANCREATIC JUICE.
(Daily Fat Ingestion, 100 Grams.)

Date, 1935.	24 hr. stool contained (gm.)	Per cent fat absorption.
2/19	11.0	80.0
2/20	7.0	93.0
4/9	11.2	88.8
10/19	5.6	94.4
10/20	7.6	92.4
10/21	3.2	96.8

NOTE.—On October 19 the gastric contents contained no pepsin or acid but considerable trypsin and some lipase.

TABLE 3.—CASE 2.

E. W. Age 53. History 422738.

Diagnosis: Carcinoma papilla Vater.

First operation: July 18, 1934. Cholecystgastrostomy.

Second operation: August 21, 1934. Partial pancreatectomy, partial duodenectomy. Duodenoduodenostomy.

Death: Due to biliary tract infection. April 16, 1935.

Autopsy: No pancreatic communication with small intestine could be demonstrated.

DAILY INTESTINAL ABSORPTION IN THE ABSENCE OF PANCREATIC JUICE.

Date, 1934.	Daily ration (gm.).		Stool contained (gm.).		% absorption.	
	Protein.	Fat.	Protein.	Fat.	Protein.	Fat.
9/8	60	40	9.7	14.4	84.0	64.0
9/9	60	40	6.9	14.6	88.5	63.0
9/10	60	40	12.6	26.7	79.0	33.0
9/15	72	41	1.2	0.6	98.5	98.5
9/16	70	39				
*9/17	51	34	31.1	16.9	39.0	50.0
*9/18	63	43				
*9/19	64	40				
*9/20	66	40	26.0	15.3	60.6	61.7
*9/21	70	40				
*9/28	70	40	6.8	7.5	90.0	81.0
*9/29	70	40	16.9	18.4	76.0	54.0
*9/30	70	40	14.5	16.9	79.0	58.0
10/2	70	40	8.8	13.4	87.4	66.0
10/3	70	40	8.8	13.4	87.4	66.0
10/4	70	40	11.7	17.4	84.0	56.0
10/5	70	40	11.7	17.4	84.0	56.0
10/9	70	40	9.3	5.2	87.0	87.0
11/9	95	100	18.0	30.0	81.0	70.0
12/12	130	115	19.4	13.0	85.0	89.0

* Received 7 capsules of Holadin, a pancreatic preparation, each day.

NOTE.—Average absorption of protein and fat:

With pancreatin—protein, 70.8; fat, 62.9.

Without pancreatin—protein, 84.7; fat, 73.1.

textbook² states that when the external secretion of the pancreas is abolished in the human, a bulky, pale or white stool results, due to excess fat.

We have had several patients in whom the duodenum and part of the head of the pancreas were removed for carcinoma of the ampulla of Vater or head of the pancreas. It is safe to assume that none of these patients had pancreatic juice in their intestine. In one, this was proven at autopsy. They served as excellent subjects for the study of fat absorption in the absence of pancreatic juice (see Tables 2, 3, 4 and Fig. 1). The first case absorbed almost the entire amount of ingested fat. The second patient also absorbed considerable quantities and these became larger in the course of time so that almost normal fat absorption was obtained 4 months after the pancreatectomy. The third patient is alive but apparently requires pancreas by mouth to insure adequate fat digestion. She is gaining weight progressively.

In this connection the work of Dr. Dorothy Andersen on cystic fibrosis of the pancreas in children¹ is significant. In these cases she found complete absence of pancreatic lipase, yet 60% of the ingested fat had been hydrolyzed to fatty acids, suggesting the activity of an intestinal lipase.

TABLE 4.—CASE 3.

A. C. Age, 53. History 392089.

Diagnosis: Carcinoma of the head of the pancreas.

Operation: March 6, 1940. Partial gastrectomy, complete duodenectomy, removal of head and part of body of pancreas, anterior gastro-enterostomy, choledocho-enterostomy.

Follow-up: October 8, 1940. Gained about 13 pounds. No obvious metastases. Taking 9 capsules Holadin each day.

DAILY FAT ABSORPTION IN THE ABSENCE OF PANCREATIC JUICE.
(Daily Fat Ingestion, 75 Grams.)

Date, 1940.	Fat in grams contained in 24 hr. stool.	% fat absorption.	Pancreatin.
3/28	63.0	16.0	None
4/2	56.0	25.3	None
6/5	20.8	72.3	9 capsules
6/6	5.7	92.4	9 capsules
6/16	38.0	50.0	None
6/17	40.2	46.4	None
6/18	81.2	0	None

TABLE 5.—CASE 4.

I. A. Age 58. History 591399.

Diagnosis: Carcinoma of the ampulla of Vater.

Operation: December 11, 1939. Resection of the duodenum and part of the head of the pancreas. Gastroenterostomy. Choledocho-enterostomy.

Follow-up: January 21, 1941. Gained about 17 pounds.

DAILY FAT ABSORPTION IN THE ABSENCE OF PANCREATIC JUICE.

Date, 1941.	Grams fat ingested per day.	Grams fat recovered in stool per day.	% fat absorbed.
1/26	75	9.77	87
1/27			
1/28			

Summary. 1. The glucose assimilation curve in cases of hyperinsulinism due to tumor of the islands of Langerhans is frequently of the diabetic type.

2. Normal glucose tolerance tests were obtained in 3 patients in whom three-quarters of the pancreas had been removed. There was no obvious difficulty with food digestion or absorption.

3. Normal fat absorption is possible when no pancreatic juice enters the intestine.

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VITAMIN C IN THE TREATMENT OF DIABETES.*

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In our studies of possible vitamin deficiencies among diabetic patients, it was thought advisable to investigate vitamin C. The chemical function of vitamin C has been better understood in plant than in animal metabolism. In plants, it is generally agreed that ascorbic acid forms part of a cellular oxidation-reduction system; while most workers agree that in animal tissues glutathione occupies a rôle analogous to ascorbic acid, and that the vitamin has no part in cellular oxidation.¹³ Even though there is no proof that vitamin C enters into the cellular oxidation of carbohydrates, various experiments indicate some effect on carbohydrate metabolism in general. Since diabetes is primarily a disturbance of carbohydrate metabolism, which secondarily causes disturbances in metabolism of other foodstuffs as well, any agent which might regulate the handling of carbohydrates assumes great clinical importance.

* This study constitutes a part of the activities supported by the Espy Fund for Research in Diabetes.

In a previous study at the Diabetic Clinic, Cincinnati General Hospital, a survey of 125 diabetic patients was made with respect to their vitamin C status.⁹ No relation was found between vitamin C and the diabetic state of the patient. This present paper covers the results of ascorbic acid administration in various dosages to controlled diabetic patients in all states of vitamin C nutrition, in order to observe what effects it may have on subjective complaints and the severity of the disease.

Stepp, Schroeder and Altenburger¹² found that 300 mg. of ascorbic acid given intravenously to 17 patients, both diabetic and otherwise, invariably produced a drop in the blood sugar, in some instances as much as 20% of the starting level. Oshima⁷ demonstrated this fall in diabetic individuals only; in normal people the blood sugar remained the same. Guinea-pigs on a C-deficient diet developed a diabetic type of glucose tolerance which was corrected when vitamin C was again added to the diet.¹¹ Clinically, Pfeiffer and Scholl¹⁰ and others have found that when ascorbic acid is given orally, the urinary sugar of diabetics is reduced and less insulin is required.

Hirsh⁵ administered vitamin C to guinea-pigs and produced an increase in liver glycogen; furthermore, this vitamin offsets the glycogenolytic activity of thyroid extract. Bartelheimer has also stated that glycogen storage in experimental animals is increased after vitamin C.¹ This is of particular interest in relation to diabetes, since many physiologists believe that the primary defect in the diabetic individual is an inability to form and store glycogen. Any agent that promotes glycogenesis and has an action similar to that of insulin might be of practical importance.

Most of the work done on the relation of vitamin C to carbohydrate metabolism has been either to measure the immediate effects of a single intravenous or oral dose, or to follow the effects of vitamin C on diabetics who have come under recent control. One group of workers whose work is widely quoted administered ascorbic acid to a group of uncontrolled diabetics at the same time that a diabetic regimen was started. They disregarded the fact that the tolerance of any diabetic patient improves under treatment, and attributed the beneficial effects to the use of the vitamin. Small laboratory animals have also been used to test the effects of ascorbic acid; but these animals are notoriously prone to show a variety of manifestations, when placed on deficient diets, which would tend to upset their carbohydrate metabolism and make estimation of the results difficult. Since many authors have intimated that vitamin C may be of some practical benefit in the treatment of diabetes mellitus, and since few reports concerning the efficacy of the vitamin appear in the literature, it is the purpose of this paper to discuss the practical benefit actually derived from the administration of various dosages of vitamin C to diabetics over a considerable period of time.

Method of Study. A group of 16 out-patients from the Diabetic Clinic of the Cincinnati General Hospital were taken for this study. Selection was made from those who were willing to cooperate and follow dietary instructions. One colored and 15 white patients were chosen. The average age was 50.8 years, the extremes being 32 and 60 years. All were taking insulin. The observations extended from February to June, 1940.

All of the patients had been controlled in the clinic for 2 to 8 years, with the exception of 2 relatively new patients who had been followed for only 4 and 6 months respectively. They were included since they were quite stable at the time the study was started. It was felt that the selection of these 16 patients eliminated the variable factor of the natural tendency of diabetics to show improvement and decreased insulin requirement early in the period of diabetic control. The length of control was discussed in a previous paper,⁸ and its importance cannot be overemphasized.

The diet allowed during the study was the same as had been prescribed for a considerable time previous to the test period. The calories ranged from 1430 to 2300 daily, and the carbohydrate from 100 to 180 gm. Each patient was asked to keep a daily record of all the food eaten, both with respect to type and amount of vegetable, fruit, or meat. The sizes of portions were recorded in common household measurements, and the diets were evaluated first for *dependable* sources of vitamin such as citrus fruits, tomato juice, and raw vegetables, and then for *uncertain* sources such as cooked fruits and vegetables. The table compiled by Bessey² was used for estimating the vitamin C content of the various foods. Dependable and uncertain sources were calculated separately and then divided by the number of days the diet was observed, so that the final figures represent the average daily intake from all sources. The theoretical amount of vitamin C that any one diet would allow by proper selection of foods was also calculated, so that two dietary vitamin C figures were available for analysis: 1, the amount that could reasonably be obtained from the diet allowed; 2, the amount actually eaten by the patient.

Before any specific medication was given, a physical examination was made with particular attention to the presence of any signs of scurvy. Examination of the gums and capillary resistance tests were made. Two of the patients had generalized arteriosclerosis with hypertension; 4 had retinitis, and 8 out of the 16 had cataracts, either operated or unoperated. In no case was there a severe infection.

At the beginning of the period, a 1000-mg. 5-hour intravenous saturation test was done. This test was described by Ludden and Wright⁶ and was designed to measure the 24-hour output of vitamin C after an intravenous test dose, based on the calculation of the 1½- and 5-hour urinary excretion. Initial blood ascorbic acid level was also measured. The method of Harris was used⁴ for the determination of the urine C, and all values were reported in milligrams.

Patients were seen in clinic every 2 to 3 weeks during the time the ascorbic acid was being given. They were weighed at each clinic visit, so that it was possible to follow weight curves during the vitamin administration; and any change in subjective complaints were elicited without the use of leading questions.

Blood sugar determinations were made at the beginning of the study and found to be within reasonable limits. The control of the diabetic state of these patients was observed by examination of the usual 4 daily routine specimens, and by measurement of the blood sugar whenever it was felt necessary. All of the patients remained under good control, as is evidenced by the fact that only 2 showed more than a 2+ sugar during the period of observation. Both instances resulted from glucose ingestion taken to correct mild insulin reaction. The urines of most of the patients were negative except for an occasional trace of sugar after meals, a finding which we consider normal in patients taking protamine insulin. Changes in the

insulin requirement were watched carefully, as this was one of the indices used to measure the effect of the vitamin.

Ascorbic acid tablets were given 3 times a day before meals,* 300, 600, and 1200 mg. being taken daily. The blood levels of ascorbic acid were examined on each clinic visit. No ascorbic acid tablets or foods that contained any appreciable amount of vitamin C were allowed on the morning of blood level determination. The method of Farmer and Apt was used for the blood ascorbic acid level.³

Results and Discussion. *Diet Analysis for Vitamin C Content.* Dietary values for carbohydrate, protein, and fat for each patient, theoretical amounts of vitamin C that the diets might reasonably be said to contain, and amounts of C actually eaten by the patients are given in Table 1. If proper selection were made, the dependable sources of vitamin C citrus fruits, tomato juice, and raw vegetables were alone sufficient to cover the daily needs. When the amount

TABLE 1.—ANALYSIS OF CARBOHYDRATE, PROTEIN AND FAT AVAILABLE AND ACTUAL VITAMIN C CONTENT OF DIETS.

Patient.	Diet.				Total vitamin C (mg.).			
	Carbo- hydrate (gm.).	Proteins (gm.).	Fats (gm.).	Calories.	Available.*		Actually eaten.	
					Depend- able.	Uncer- tain.	Depend- able.	Uncer- tain.
1	165	85	125	2125	100	40	41	57
2	160	70	80	1740	100	40	45	30
3	150	80	100	1820	90	25	0	46
4	150	75	60	1440	90	25	64	61
5	180	80	140	2300	100	40	24	38
6	120	70	115	1795	50	20	80	40
7	130	70	70	1430	50	20	3	20
8	150	75	75	1575	90	25	40	30
9	130	75	85	1585	50	20	80	75
10	160	70	60	1560	100	40	0	19
11	150	80	60	1560	90	25	65	35
12	135	70	100	1700	50	20	0	60
13	160	80	80	1680	100	40	0	25
14	140	60	70	1430	90	25	76	25
15	150	85	140	2190	90	25	40	45
16	100	65	90	1470	50	20	76	35

* Average figures for the common fruits and vegetables.

that is inconstantly present in cooked fruits and vegetables was added, there was a considerable margin of safety. It is entirely possible to design diabetic diets having an adequate amount of vitamin C, if foods with a high natural content of C are chosen. In all but three instances in which the diet was analyzed, the theoretical amount of vitamin the prescribed diet could reasonably contain was higher than the amount eaten. Since all patients received regular instruction about selection of foods, in order that the greatest value per dollar could be obtained, we feel that dietary lack of vitamin C was mainly dependent on likes and dislikes of the patient or improper handling and cooking of foods.

Weight Changes. Of the 16 patients who were on 300 mg. of ascorbic acid daily, 2 lost 5 pounds over a period of 3 weeks, and

* The ascorbic acid for this study was supplied through the courtesy of Parke, Davis & Co.

1 gained 5 pounds over a period of 5 weeks. With the larger doses of 600 and 1200 mg., 1 gained 3 pounds and 1 lost 3. These observations failed to demonstrate any consistent weight change.

The insulin requirement was followed very carefully, because reports in the literature state that the administration of ascorbic acid lessens the insulin need. An effort was made to keep constant all variable factors such as diet, exercise, worry, and infections. During the whole period of observation, only 2 patients needed a significant change in insulin dosage: 1 needed an increase of 8 units, and 1 a decrease of 10. It seems safe to say that ascorbic acid does not consistently alter the insulin requirement in previously well-controlled diabetic patients, as long as their dietary intake remains constant.

Ascorbic acid saturation tests and blood ascorbic acid determinations were made on each patient at the beginning of the period of administration to determine their state of vitamin C nutrition. Although no signs of scurvy were found among any of the patients, 7 of the 16 were found to have fasting blood ascorbic acid values below the so-called scurvy level of 0.4 mg. per 100 cc. Two had levels between 0.4 and 0.8 mg. per 100 cc., and the remaining 7 had levels over 0.8 mg. per 100 cc. A fairly close correlation was found between the blood ascorbic acid level and the milligrams excreted after an intravenous test dose. Of the patients with chemical scurvy, all but 1 had a urinary output of less than 400 mg. after an intravenous test dose of 1000 mg. Of those with blood levels over 0.4 mg. per 100 cc., only 1 failed to excrete less than 400 mg. Since such a close parallel existed between the blood ascorbic acid and the urinary output in the saturation tests, the patients were subsequently followed by measurement of the blood levels alone.

Effect of 300 Mg. Ascorbic Acid on the Blood Levels. In every instance the blood levels rose after the administration of 300 mg. ascorbic acid daily. Whereas a striking increase was found among patients who started with low levels, many of those with a good state of saturation also showed a marked rise. The greatest single increase was found in a patient who started with a blood ascorbic acid of 1 mg. per 100 cc. (Table 2, No. 13). A prolonged accumulative effect from the administration of the vitamin could not be demonstrated. Those who took 300 mg. of ascorbic acid daily for longer than 3 weeks showed lower levels of blood ascorbic acid at the end of the period than those who took it for less than 3 weeks. In observing patients from week to week, the highest levels were found on the first visit after the medication was started; there would then be a slow, progressive fall, even though administration was continued in the same dosage.

The Effect of 600 and 1200 Mg. Ascorbic Acid on the Blood Levels. Ascorbic acid was increased to 600 or 1200 mg. daily immediately after the 300-mg. dosage was discontinued. In spite of the fact that the amount was doubled or quadrupled, no significant changes

could be demonstrated. Six patients showed a rise in blood ascorbic acid levels, 7 showed a drop, and 2 stayed the same. These results indicate that a state of saturation can be reached with a comparatively small dose, and that once it is reached, no further increase in the blood level can be attained. Excretion then matches ingestion.

TABLE 2.—EFFECT OF VARIOUS DOSAGES OF VITAMIN C ON WEIGHT,* INSULIN REQUIREMENT, AND NON-SPECIFIC SYMPTOMS.

Patient.	Sex.	Age.	Vitamin C.										Non-specific symptoms.		
			Weight, pounds.		Insulin, units.		Saturation test.		Blood, mg. per 100 cc.		Daily dosage, mg.	Weeks given.			
							Beginning.	End.	Blood, mg. per 100 cc.	Total excreted in urine, mg.				Beginning.	End.
300 Mg. DAILY DOSAGE.															
1	F	53	114	115	25	22	0.05	296	0.05	1.11	300	3	+		
2	F	41	146	146	30	35	0.15	238	0.15	1.15	300	3	0		
3	M	48	130	130	70	70	0.15	377	0.15	1.27	300	4	0		
4	M	60	139	139	100	100	0.19	260	0.19	1.07	300	3	0		
5	M	58	140	135	35	35	0.22	196	0.22	1.04	300	3	+		
6	M	58	139	120	17	17	0.31	413	0.31	1.08	300	5	+		
7	F	53	138	136	22	22	0.37	291	0.37	0.98	300	3	0		
8	F	56	132	132	40	40	0.48	405	0.48	1.24	300	3	+		
9	F	60	126	127	34	34	0.50	760	0.50	1.30	300	7	+		
10	M	36	174	169	60	60	0.80	653	0.80	1.22	300	3	+		
11	M	40	146	144	30	30	0.81	708	0.81	0.94	300	3	+		
12	M	57	115	120	22	22	0.96	712	0.96	1.33	300	5	+		
13	F	56	119	117	25	25	1.00	588	1.00	2.56	300	2	+		
14	F	58	116	118	16	16	1.00	734	1.00	1.10	300	8	+		
15	M	32	124	123	50	50	1.13	372	1.13	1.24	300	3	+		
16	F	57	128	130	12	12	1.56	744	1.56	2.15	300	3	+		
600 Mg. DAILY DOSAGE.															
11	M	40	144	144	30	30			0.94	0.80	600	2			
7	F	53	136	136	22	30			0.98	0.88	600	4			
5	M	58	135	134	35	32			1.04	1.27	600	4			
4	M	60	139	139	100	100			1.07	1.24	600	2			
6	M	58	129	127	17	17			1.08	1.42	600	4			
14	F	58	118	119	16	16			1.10	0.65	600	3			
10	M	35	169	169	60	60			1.22	1.56	600	4			
9	F	60	127	127	34	34			1.30	1.24	600	2			
12	M	57	120	117	22	22			1.33	1.33	600	4			
3	M	48	130	130	70	60			1.37	1.22	600	5			
16	F	57	130	133	12	10			2.15	1.10	600	4			
1200 Mg. DAILY DOSAGE.															
2	F	41	146	147	35	38			1.15	1.15	1200	1			
15	M	32	123	123	50	50			1.24	1.68	1200	1			
9	F	60	127	126	34	34			1.24	1.15	1200	1			
8	F	56	132	134	40	40			1.24	1.68	1200	2			

* For diet see Table 1.

Analysis of Subjective Complaints. Since there were no signs of ascorbic acid deficiency, only subjective indices of a general nature could be measured. Nine patients felt better after taking the medication, 5 felt the same, and 2 felt worse. Of the 9 that felt better, 1 who had cataracts noticed an improvement in vision; the remaining 8 noticed an increase in body strength and endurance. It was felt that this improvement had nothing to do with the specific medication, because the greatest improvement was found among those who started with a good state of vitamin C nutrition. Among those patients with chemical scurvy in whom the greatest improvement could be expected, 2 felt better, 3 noticed no change, and 2 felt worse after taking ascorbic acid.

In spite of the fact that there is experimental evidence to show that ascorbic acid has a beneficial effect on the ability of the normal and diabetic individual to metabolize glucose and store glycogen, no practical benefit resulted from its administration. We feel that the best way to assure adequate intake of vitamin C in diabetic patients is by instruction in the proper selection of foods having a high natural content. Supplemental additions of ascorbic acid appear to have no beneficial effect on the diabetic state.

Summary. 1. Ascorbic acid was administered in 300, 600 and 1200 mg. daily doses to 16 diabetic patients in various states of vitamin C nutrition. All patients had been under good control, and were kept as stable as possible during the period of observation.

2. No constant objective improvement resulted from the ascorbic acid administration in any dosage or for any length of time. There was no weight gain or significant change in the insulin requirement. The disease severity remained unchanged.

3. Some subjective improvement, consisting of increased strength and endurance, was found in 9 of the 16, but the least improvement was found among those who started with a poor state of vitamin C nutrition.

4. Regardless of the initial state of vitamin C nutrition, ascorbic acid administration has no effect on the severity of the diabetic state.

The authors are indebted to Dr. C. A. Mills for his constructive suggestions and criticism during the course of the study and in the preparation of the manuscript.

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SOME EFFECTS OF IRON ON HEMOGLOBIN FORMATION.

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ALTHOUGH the efficacy of simple iron salts in the treatment of iron deficiency hypochromic anemias is well recognized there are

many unsolved problems in regard to their utilization and mode of action. A more rapid increase in the blood hemoglobin has been noted with the use of excessive amounts of iron than with smaller but apparently adequate amounts. The reason for this has not been satisfactorily explained. Balance studies have shown that a large amount of the administered iron is retained by the body, but in spite of this large retention only a small percentage is utilized immediately in hemoglobin formation, so that a sufficient amount of iron should remain in the tissues for continued hemoglobin increase if this iron is in a utilizable form.^{2,3} One might expect, therefore, a continuing rise in the blood hemoglobin after iron therapy has been discontinued, but it is well recognized that in many cases of iron deficiency anemia it is necessary to continue iron medication indefinitely in order to maintain the hemoglobin at its normal level, even though all apparent causes for the anemia have been removed. This maintenance dose of iron need not be as large as that necessary to bring the hemoglobin up to the normal level but must be administered continuously or intermittently for indefinite periods.

During previous balance studies it was found that when 1 gm. of iron and ammonium citrates was administered per day 26.6% of the elemental iron was retained, but only 9.3% was utilized in hemoglobin formation.³ This means that an average of approximately 37 mg. of iron per day was being stored and we have shown that this storage continues over a long period of time. Where, and in what form, this iron is stored in the body was not determined, but if it is in a utilizable form it should provide adequate iron for continued hemoglobin formation.

This same amount of iron and ammonium citrates, 1 gm. per day, was administered to a group of 12 individuals for a period of 60 days. The subjects for this study were young adults, students and nurses at the University Hospitals, who were healthy except for the mild anemia which was detected on routine examination. None was included who had had a recent hemorrhage, infection, or other illness to account for the anemia. The blood hemoglobin varied from 8.68 to 11.78 gm. per 100 cc., the hematocrit values ranged from 34 to 44%, and the erythrocyte counts from 3,670,000 to 4,800,000 per c.mm. Hemoglobin determinations were done by the Newcomer method,⁶ adequately checked by oxygen capacity; the hematocrit values were determined by the Van Allen method,⁷ and the erythrocyte counts were done with instruments certified by the United States Bureau of Standards. Each of these determinations was done at approximately 2-week intervals.

Following the administration of iron and ammonium citrates for 60 days the medication was discontinued, but the observations on the blood were continued at the same intervals for periods up to 26 weeks. Some of the subjects stopped reporting for the blood examinations after varying periods of time, as can be seen in the table, so that the averages computed for the later periods are

determined from a smaller number of cases. In the table the averages of the initial blood findings for each group of cases are recorded together with the subsequent average hemoglobin value and the number of patients from which each average is derived. The average hemoglobin gain at 2-week intervals is shown graphically in the charts.

IRON AND AMMONIUM CITRATES

1 GRAM DAILY FOR 60 DAYS

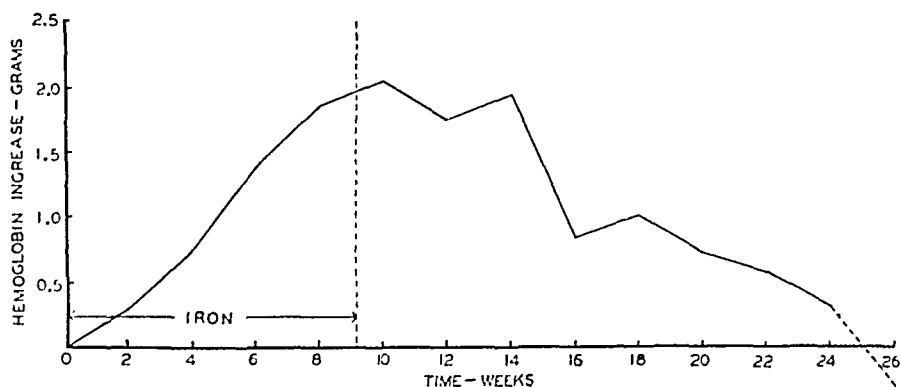


CHART I.

REDUCED IRON

1 GRAM DAILY FOR 60 DAYS

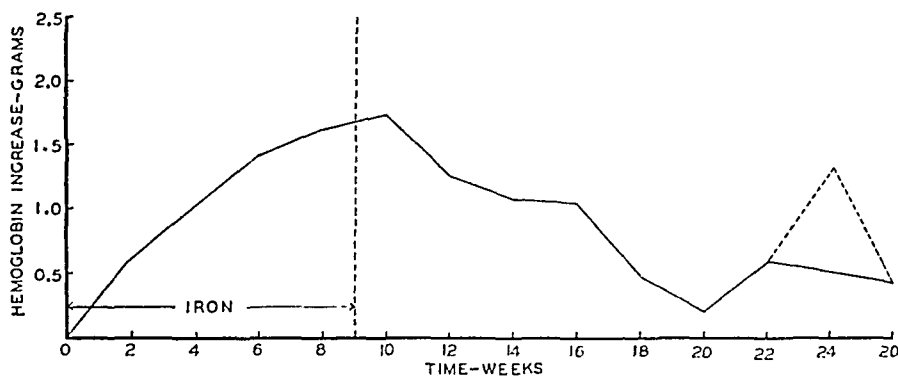


CHART II.

As may be seen in Chart I, there was a gradual increase in the blood hemoglobin during the period of iron administration and continuing for a short period thereafter; so that the peak of hemoglobin regeneration occurred at the 10th week even though iron therapy was discontinued after the 60th day. Following this there was a gradual decrease in the blood hemoglobin, so that the average values had returned to approximately the pre-treatment level by the 26th week.

A similar study was carried out on a group of 13 cases who received 1 gm. of reduced iron per day for 60 days. This preparation contains a higher percentage of metallic iron than do iron and ammonium citrates but it is in a more insoluble form. The blood hemoglobin in this group ranged from 8.68 to 10.94 gm. per 100 cc. with an average value of 10.17 gm. for the entire group. The hematocrits ranged from 33 to 43% and the erythrocyte counts from 3,860,000 to 4,590,000. The procedures were the same as with the preceding group and the hemoglobin response was almost identical as is shown in Chart II. The hemoglobin gradually increased to reach its peak in the 10th week, and then fell to the pre-treatment level after 26 weeks.

In spite of the fact that balance studies had shown a retention of sufficient iron to provide for future hemoglobin regeneration, it would seem logical to explain this fall in hemoglobin to the discontinuation of iron therapy. However, two other groups of subjects with similar hemoglobin levels were followed in the same manner but were given iron continuously throughout the period of observation. To one group was given 1 gm. of iron and ammonium citrates per day and to the other 1 gm. of reduced iron. The average blood hemoglobin level for the 15 individuals receiving iron and ammonium citrates was 11.53 gm. It will be noted in Chart III that the same type of response occurred as in those receiving iron for only 60 days, the peak in the hemoglobin regeneration coming on the 12th week and following this there was a gradual fall. The hemoglobin did not quite drop to the pre-treatment reading, as the average hemoglobin for the group leveled off at a point representing a gain of 0.9 gm. In 7 subjects (average hemoglobin 11.36 gm.) who were given reduced iron the hemoglobin response was practically the same with the peak at 10 weeks followed by a decline to a level which was nearly that which obtained before treatment (Chart IV).

The similarity of the hemoglobin curves in those subjects receiving iron for 60 days and in those receiving iron continuously is striking. In both cases the peak in hemoglobin regeneration occurred in the 10th or 12th week and was followed by a steady regression in the blood hemoglobin to near the pre-treatment level. The rate of regression was nearly the same in both instances. That this uniform fall in hemoglobin is not an artefact produced by charting average values is seen by following hemoglobin levels in individual cases and is the type of response reported by Widdowson and McCance following iron therapy.⁹

In following the results in individual cases it is found that two distinct types of response are obtained. In both types there is the same initial hemoglobin increase but in one group, which includes a majority of the subjects, the hemoglobin subsequently falls to the pre-treatment level. In a second smaller group of cases the hemoglobin drops after the initial rise but remains from 1 to 2 gm. above

the pre-treatment level. Both types of curves occurred in subjects receiving treatment for 60 days as well as in those receiving iron continuously, although in the latter group the persistent increase tended to be higher. No prediction could be made from the original hemoglobin level as to which type of response would occur in a given case since certain cases showing a persistent elevation had original

IRON AND AMMONIUM CITRATES

1 GRAM DAILY - CONTINUOUS

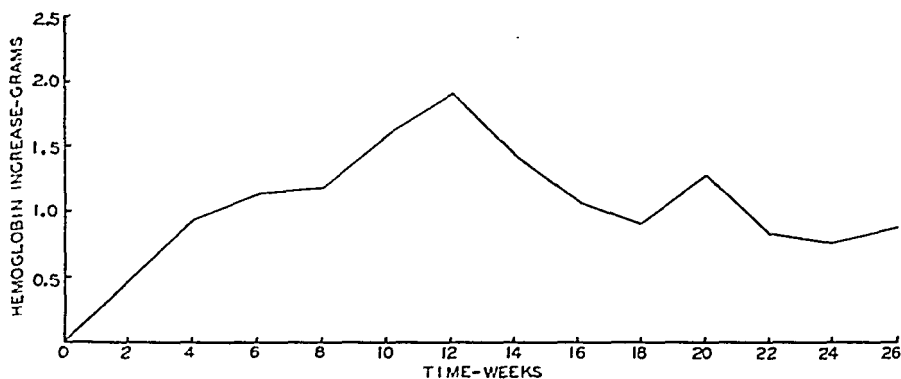


CHART III.

REDUCED IRON

1 GRAM DAILY - CONTINUOUS

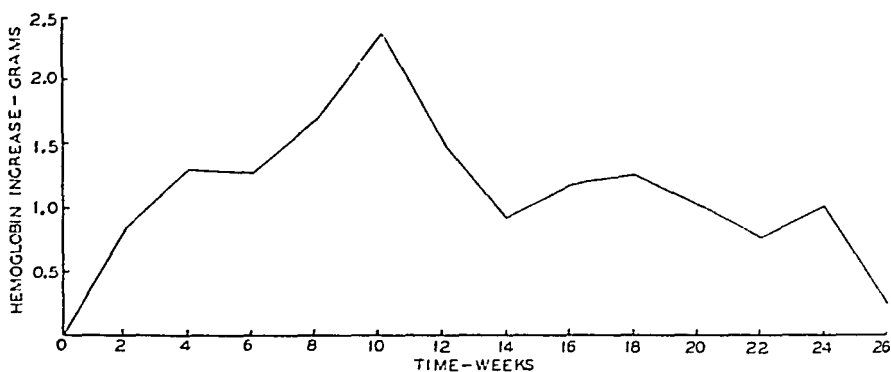


CHART IV.

blood hemoglobins as high as other cases in which the hemoglobin fell to the pre-treatment level. In spite of this fact one is tempted to classify those with a persistent elevation as cases of mild anemia and those in which the hemoglobin fell to the pre-treatment level as cases whose hemoglobin is in a low normal group. Such a classification is used in Charts V and VI which depict the types of curves mentioned for the two groups of cases. This interpretation presupposes that

each individual has a hemoglobin level which is normal for him or herself, but that this normal varies from one individual to another so that a reading which is normal for one individual may represent a mild degree of anemia in another. Such a view is in keeping with the numerous, apparently low, hemoglobin readings which we have

EFFECT OF IRON ON MILD ANEMIA

THE HEMOGLOBIN REMAINS ELEVATED ABOVE THE PRETREATMENT LEVEL

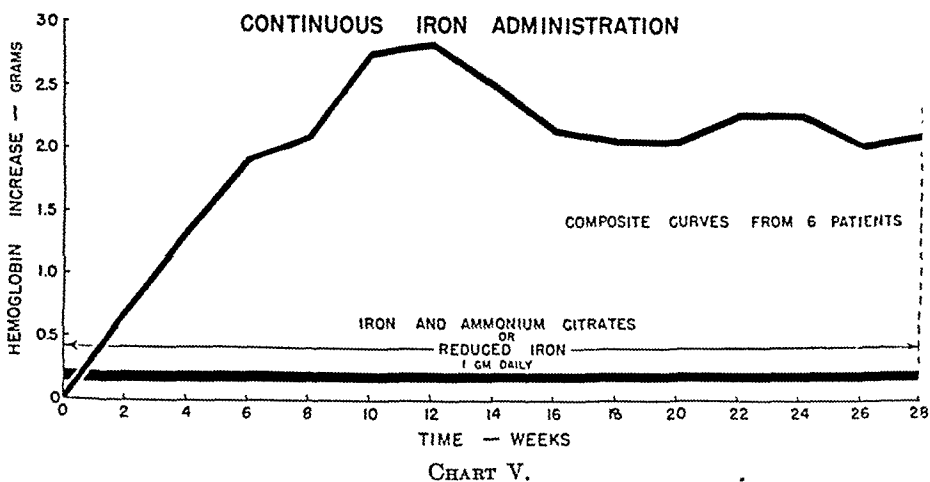
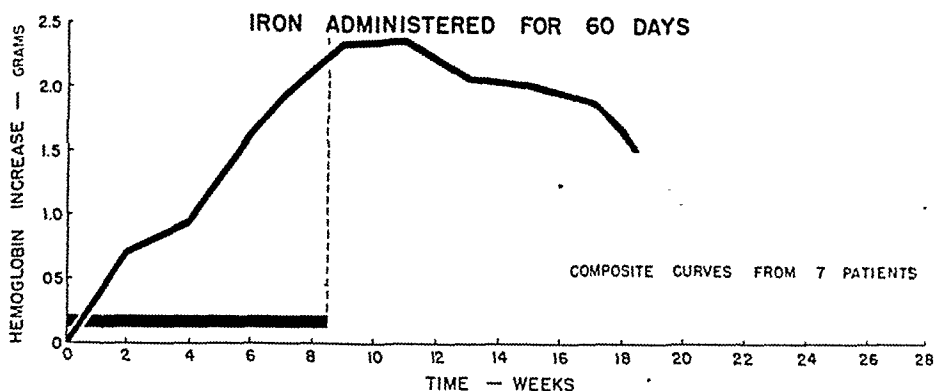


CHART V.

Smoothed composite curves from averages of selected cases. Upper curve from Cases 4, 6, 7, 9 and 12 in Group I and Cases 9 and 10 from Group II. The first group received iron and ammonium citrates and the second group reduced iron, 1 gm. per day. Lower curve from Cases 5, 6, 13 and 15 in Group III, and Cases 2 and 6 in Group IV.

encountered in otherwise healthy individuals and also provides the most logical explanation for the variation in the response to iron therapy. If this is true, many patients heretofore considered to have a mild anemia in reality have hemoglobin values which are normal for them. Many hemoglobin values which we have placed in the

low normal group are considerably below the usually accepted normal values.

The most striking feature in these curves is the decrease in hemoglobin after an initial rise and the fact that it occurs regardless of whether or not iron medication is given continuously and regardless of the final hemoglobin level. This suggests that iron is not acting

EFFECT OF IRON ON LOW NORMAL HEMOGLOBIN THE HEMOGLOBIN RETURNS TO THE PRETREATMENT LEVEL

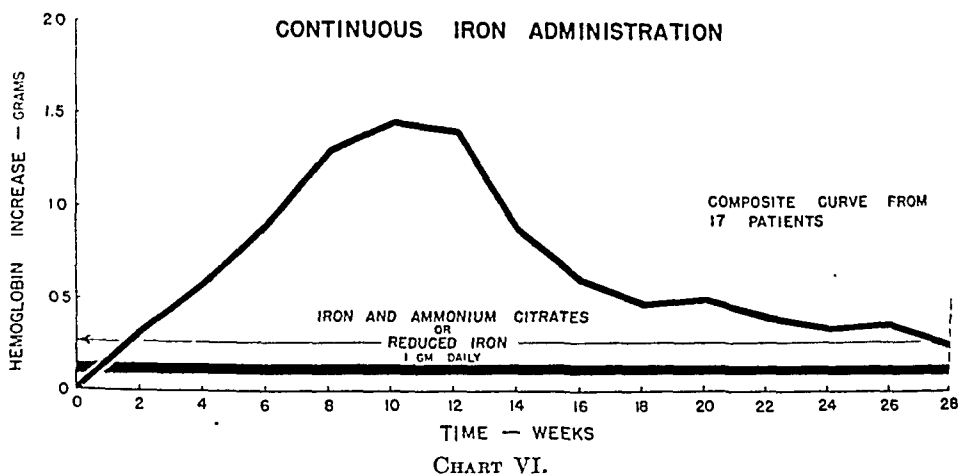
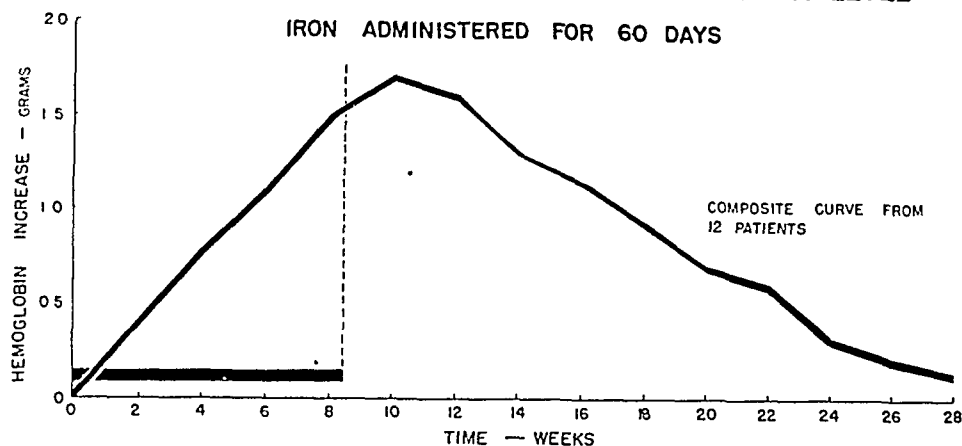


CHART VI.

Smoothed composite curves from the averages of all cases in the four groups not included in Chart V.

entirely as a form of replacement therapy but that it has an additional stimulating effect. This is evidenced by the fact that the hemoglobin falls from its peak in spite of the continued administration of iron and that even in those individuals showing a permanent elevation there is a preceding peak and regression. The dosage of iron employed was relatively small as compared to the usually

recommended dose of iron salts but is sufficient to supply an overabundance of iron for hemoglobin formation as well as an additional amount for storage. It is known that large amounts of iron cause a more rapid hemoglobin regeneration than do smaller amounts, but the reason for this greater response has not been adequately explained except by supposing a "salt" or catalytic effect.⁸ Moore⁵ has demonstrated an increase in the blood serum iron after iron therapy and has shown that the increase is greater with larger doses of iron. Experiments with radioactive iron salts have apparently demonstrated the presence of this radioactive iron in the erythrocytes within a few hours.^{1,4} It seems probable from these experiments that the iron is taken directly from the blood stream and with

IRON AND AMMONIUM CITRATES

1 GRAM DAILY - CONTINUOUS

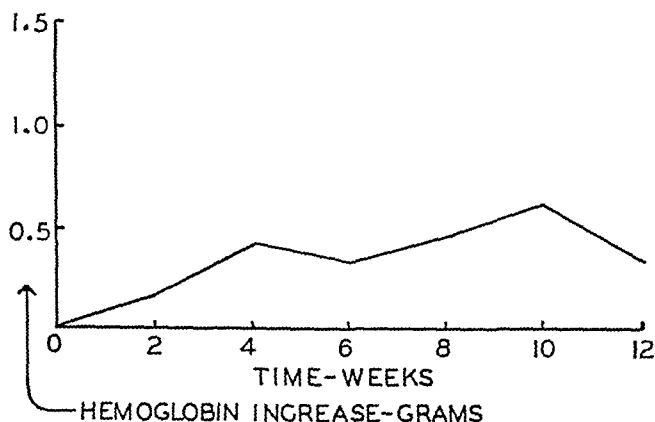


CHART VII.

a larger amount of iron available, hemoglobin is formed more easily and more rapidly, so that the greater response to larger doses is merely due to the availability of larger amounts of iron. This is not the entire picture, however, since the serum iron curves drop rapidly to normal after a few hours and we have shown that the hemoglobin continues its rapid response for 10 to 14 days after iron medication has been discontinued. We do not feel that the changes in the blood serum iron can explain all of the features.

If iron has a stimulating effect on hemoglobin formation in addition to its action as replacement therapy, there should be a response in individuals whose blood hemoglobin levels are relatively high. To test this, a group of 12 male subjects with hemoglobin values ranging from 13.33 to 15.74 gm. per 100 cc. were given 1 gm. of iron and ammonium citrates per day. The hemoglobin response in this group was not great, but the average values for the entire group

show an increase, and the contour of the plotted curve is similar to that obtained in subjects with lower blood hemoglobin values although the changes are less extensive (Chart VII). There is a variation in the individual responses but the average response corresponds so closely to the previous curves that we feel it is of significance as evidence of mild stimulation.

Group.	Medication.			Control.				
		Daily dosage, gm.	Duration.	No. sub-jects.	Av. R.B.C.	Av. hemat., %.	Hemoglobin.	
							Av., gm.	Range, gm.
I	Iron and ammonium citrates	1	60 days	12	4.18	38	10.32	8.68-11.78
II	Reduced iron	1	60 days	13	4.28	37	10.17	8.68-10.94
III	Iron and ammonium citrates	1	Continuous	15	4.81	41	11.53	10.22-14.38
IV	Reduced iron	1	Continuous	7	5.19	42	11.36	8.45-13.75
V	Iron and ammonium citrates	1	Continuous	12	..	46	14.17	13.33-15.74

	2 weeks.		4 weeks.		6 weeks.		8 weeks.		10 weeks.		12 weeks.		14 weeks.	
	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.
Group I	10	10.60	10	11.05	11	11.73	11	12.17	8	12.39	7	12.15	4	12.20
Group II	11	10.76	10	11.19	13	11.60	10	11.74	10	11.85	6	11.69	9	11.29
Group III	14	12.02	14	12.51	14	12.77	10	12.70	9	12.67	15	13.36	9	12.69
Group IV	6	12.08	7	12.64	5	13.07	3	12.04	4	13.13	5	13.19	4	12.57
Group V	10	14.40	6	14.72	8	14.60	6	14.92	6	14.94	6	14.53

	16 weeks.		18 weeks.		20 weeks.		22 weeks.		24 weeks.		26 weeks.	
	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.	No. sub-jects.	Av. Hb., gm.
Group I	8	11.52	6	11.02	7	10.95	3	10.81	2	10.94	1	10.52
Group II	6	11.11	2	11.05	3	10.65	3	11.01	2	10.79	1	11.36
Group III	12	12.57	10	12.44	9	12.44	9	11.76	7	11.74	6	11.78
Group IV	5	12.17	4	12.01	4	12.27	4	11.47	3	11.78	1	10.94
Group V

The original detailed tables have been condensed to the present form to conserve space.

Summary and Conclusions. Iron and ammonium citrates and reduced iron produce an increase in the blood hemoglobin which reaches a peak at the end of 10 to 12 weeks. Following this peak there is a gradual reduction in the hemoglobin level regardless of

whether or not the iron is given for a period of 60 days or continuously throughout the period of observation.

The increase in hemoglobin, the peak, and subsequent reduction are similar in patients with mild grades of anemia and in individuals with low normal hemoglobins, although in the latter group the hemoglobin falls to the pre-treatment level, whereas in the former it remains elevated but at a level below the point of maximum response.

A similar but less marked hemoglobin response is obtained in subjects with high hemoglobin values.

These results suggest a stimulating action of iron on hemoglobin formation in addition to its action as replacement therapy.

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THE QUESTION OF "CHRONIC APPENDICITIS."*

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A MAN 27 years old, possessed of much too fine sensibilities, presented himself as a patient 15 years ago. Except for this one personality defect he was extremely fortunate in birth and all the circumstances of life. He mentioned an occasional sick headache which he took for granted. The complaints for which he sought medical aid related to digestion—gas on stomach with some eructations, feeling of epigastric pressure after meals, intractable constipation, and vomiting on arising on an average of 3 mornings a week. These symptoms began at age 15 in boarding school, and in varying grades of severity had been present ever since, except for one period of 18 months. This was when he was in the army.

This patient passed a splendid physical examination, and in the laboratory nothing abnormal was found, not even a gastric hyperacidity. The gastro-intestinal Roentgen ray studies showed no abnormality in the stomach or small intestine. This additional note was made, "The appendix is seen. It is retrocecal, drains poorly, and shows some evidence of adhesions near the tip. There is some retention after 96 hours, following catharsis. It is believed to be pathologic. The ascending colon is redundant and the cecum

* Read before the American Clinical and Climatological Association held at White Sulphur Springs, Va., October 28-30, 1940.

is low, but shows no evidence of adhesions. There is moderate colonic stasis, a large portion of the barium being retained at 72 hours."

Treatment consisted of suggestions as to diet and an attitude toward life, belladonna, bromides, and the cautious use of cathartics. Recovery was prompt and complete, but not lasting. Six months later, following the illness of his wife with eclampsia, all symptoms returned. The stools at this time, obtained with difficulty, were hard scybala covered with mucus. When assured of the complete recovery of his wife, the same therapeutic measures which had been employed on earlier attacks were promptly effective. Two years later toward the end of his wife's next pregnancy, an attack recurred which lasted until the delivery, without episode, of a normal full-term infant. There was now 60 acidity per cent free acid in the fasting stomach contents, and the stools were entirely characteristic of mucous colitis. Severe, though not disastrous, financial reverses during the first "depression," the death of his mother and lingering fatal illness of his father-in-law, were taken in stride with but minor upsets easily controlled.

Five years ago this patient's case was studied at another hospital. The findings were essentially the same as ours on his original examination 10 years before. An appendectomy was advised and carried out following which the patient took 2 months' vacation. He and his family were delighted that all his symptoms were relieved. Six months later he returned to my office with the old symptoms which he had had for the preceding 2 weeks. The enforced vacation after what he accepted as an unavoidable operation, had given him an "out" from his personal responsibilities; the way the army period presumably had done. His responsibilities were no greater than those incidental to normal living but he carried them very laboriously. Much advice about learning to live quietly in his environment, some belladonna, and enough bromides, relieved again. This was 5 years ago. He is now 42 years old and doing better, but still having attacks.

This is a characteristic case. Repeated disappointments after appendectomy in similar ones led to further study of the problem.

Three series of 100 consecutive cases on the ward, and 2 similar series in the office were questioned particularly about earlier appendectomies. If a patient reported an attack sudden in onset with prompt removal of the appendix, the case was regarded as acute. The case was classified as "chronic" if the appendix had been removed only after a diagnostic survey. Patients in the chronic group were then asked for what symptoms the operation had been done, if relief resulted, and a note was made on the present diagnosis.

Forty-four appendectomies were recorded for the 300 ward patients (14.6%). Twenty of these were acute, 16 were removed as routine during pelvic operations, and 8 were classified as "chronic."

Of ward patients, 2.6% had been operated upon for so-called chronic appendicitis from 2 to 37 years before.

Fifty appendectomies were recorded for the 200 private patients (25%). Thirty-five of these were acute, 6 were removed as routine at other abdominal operations, and 12 were classified as "chronic," the operation performed from one-fourth to 25 years ago. Six per cent of private patients had been operated upon for so-called chronic appendicitis.

It is believed this series of patients is long enough to have some statistical value. Broken down into consecutive series of 100 the percentages for each approach each other closely. The 14.6% of ward patients who had appendectomies, 2.6% of which were for so-called chronic appendicitis, is to be compared with 25% of private patients who had had appendectomies, 6% of which were chronic. This comparison in itself may have significance. Particularly one might note that operation for chronic appendicitis in this series was recorded more than twice as often in the histories of private patients as in those of ward patients.

Two of the 8 ward patients in the chronic appendectomy series were permanently relieved, one of frequent attacks of nausea and another of abdominal pain. This latter might have been acute appendicitis. The remaining 6 ward patients all operated upon for digestive disorders or other abdominal symptoms denied relief following the appendectomy. The present diagnoses on these patients were ureteral colic, tabetic crisis, pulmonary tuberculosis, thyrotoxicosis, cardiovascular-renal disease, and recurrent rheumatic fever. Note the definite diagnosis possible in these 6 ward patients, to be compared later to those made in the 12 private patients.

One of the 12 private patients was a boy 8 years old who, 3 months before, had lost his appendix because of a fever of 6 months' duration, although he had never had an attack of appendicitis. The fever persisted, a possible but not proven case of undulant fever. Another was a man 48 years old who had had the operation 8 years earlier for migraine, without relief. The remaining 10 of the 12 private patients submitted to appendectomy for digestive disorders. Not one was relieved. The indigestion had persisted for from 4 to 25 years after the operation. It is this group of patients I wish to emphasize.

There was a total of 20 cases in the two series, 2 of which, both ward patients, claimed relief; and 6 of which, all ward patients, although not relieved, could be given definite objective diagnoses. Two only of the 10 private patients, operated upon for relief of digestive disorders could be given a definite diagnosis at the time of the present study. A woman 58 years old, 24 years after, and a man 52 years old, 9 years after the appendectomy were shown to have duodenal ulcers. Examination of the remaining 8 developed no objective diagnosis. Neurasthenia, psychasthenia, pylorospasm,

all functional, nervous indigestion if you like, was the best we could do for them.

Discussion. The uniformity of trend of these statistics is surprising. They conform closely, also, to the findings in a similar study of many more patients reported recently by Alvarez.¹

A single attack of acute appendicitis, perhaps so mild as to go unrecognized, can result in adhesions and other local deformities capable of setting up reflex disturbances of the delicately balanced motor mechanism of the upper and lower gastro-intestinal tract. Repeated disappointment with results of appendectomies in such cases, incorrectly called chronic appendicitis, and the statistics just mentioned indicate, however, that this occurs much less frequently than supposed. The scars of healed acute appendicitis as a cause of indigestion is a diagnosis made—or one might say indulged in—much too often. The hoped-for relief of indigestion after appendectomy would be realized more often if this classification were limited to those cases with a recent history of one or more attacks of what might have been an acute appendicitis, and with local signs in the region of the appendix when the symptoms of indigestion are present. These cases are not, of course, examples of chronic appendicitis. They are patients with low-grade recurrent attacks of acute appendicitis. It would seem that we might well return to our earlier conception taught by the pathologists, that true chronic appendicitis is very rare, if indeed it ever occurs. I have been unable to find an unqualified statement in any treatise on pathologic anatomy by a recognized authority that any lesions are encountered which can properly be called "chronic appendicitis."

The patient with disturbed digestion on a functional basis—old-fashioned nervous indigestion—can have, indeed are more likely than others to have, acute appendicitis. One must be careful not to miss such an attack. Each of our patients with nervous indigestion who had an attack of acute appendicitis obtained relief from the digestive disorders after the appendectomy for periods up to 1 year. Not one of these patients obtained permanent relief, all reacting exactly as those submitting to operation for chronic appendicitis.

Was Henry Thoreau a wise man or a weak one? From a life in Concord in 1845 incomparably less complex than that of today in a big city, he avoided a functional neurosis—possibly it might have had gastro-intestinal manifestations—by an escape. He refused to bear the burden of a conflict, made a choice at the right time, and abided by it as long as was necessary. Toward the end of this excellent course of treatment, planned by himself, he wrote, "Most men are in a strange uncertainty about life . . . many . . . propose to creep down the road, pushing . . . It's a fool's life, as they will find when they get to the end of it, if not before."

Would we get more cures in selected cases of indigestion by pre-

scribing a Walden Pond* than by carrying out an appendectomy on cases of suspected "chronic appendicitis"? The suggestions of this statistical study indicates that we would.

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**DEMONSTRATION THAT IN NORMAL MAN NO RESERVES OF
BLOOD ARE MOBILIZED BY EXERCISE,
EPINEPHRINE, AND HEMORRHAGE.**

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THE circulation readily compensates for a sudden increase in the size of the vascular bed in various parts of the body, or for a sudden decrease in blood volume. During exercise the vessels in the muscles dilate, the bloodflow becomes rapid, and the cardiac output increases. Additional blood is shunted from other parts of the body to the muscles to fill the dilated vascular bed. The more rapid circulation of blood already present in the extremities and muscles also causes the cardiac output to increase. A similar set of compensatory phenomena occurs when the body is heated and the vessels of the skin are dilated.

Compensatory reactions also take place when blood is rapidly removed from the body by hemorrhage or pooled in the extremities by venous congestion. Until considerable blood has been removed, the circulation at rest appears to be perfectly normal; the pulse and blood pressure show little change. During this period, either a redistribution of the blood circulating in the body occurs to make up for the blood removed from the general circulation, or new blood is added to the general circulation from blood reservoirs. Barcroft attempted to elucidate this problem by experiments on animals, and in a brilliant series of investigations demonstrated that in the cat and dog there is a reserve of red blood cells stored in the spleen which can be emptied into the general circulation in time of need.³ He showed that the spleen of the cat and dog contracted during exercise or hemorrhage, and estimated that the contraction of the

* Today a busy motor highway runs sufficiently near to the location of Walden Pond to disturb its one-time serenity by raucous noises and nervous haste. Possibly this development not only illustrates the need for escape, more today than 90 years ago, but also symbolizes the greater difficulty of its accomplishment.

spleen increased the amount of blood in the circulation 6% to 15%.⁵ It has been further demonstrated that the large increase in red cell count and hemoglobin that occurred in the normal cat and dog after fright or exercise was abolished by splenectomy.^{1,25,35b} Other workers showed that epinephrine likewise caused contraction of the spleen of the dog and increased the erythrocyte count.^{16,22,30}

Barcroft's concept of blood reservoirs was taken up with enthusiasm, and many experiments were devised to demonstrate their existence in man. It soon became apparent that the large increases in hematocrit and hemoglobin values found in the cat and dog after light exercise or after epinephrine did not occur in normal human subjects.^{14,29,39} By the blood volume methods then in use, it was found that various stimuli, such as exercise, heat, and epinephrine, produced an increase in the total blood volume with little change in hematocrit reading.^{14,24,39} As this increase in volume occurred in splenectomized as well as in normal subjects, it was concluded that other organs, such as the liver and subpapillary venous plexus of the skin, must serve as reservoirs for both red cells and plasma.

It is of fundamental importance to know whether in normal subjects there are reserves of red blood cells, or of plasma, or of both, in order (a) to understand the adjustments of the circulation during exercise, fever, dehydration and blood loss, and (b) to interpret the changes in hematocrit, hemoglobin, and serum protein values that occur in the peripheral blood in acute experiments such as exercise or administration of various drugs. It is obvious that in the presence of a reserve of red blood cells, which could be quickly mobilized and ejected into the blood stream, the hematocrit reading or hemoglobin concentration would be useless as a method for following changes in plasma volume. If there were a reserve of protein or plasma, changes in plasma protein concentration would not necessarily reflect changes in plasma volume, even in acute experiments.

According to the literature, the three most effective stimuli for mobilizing the blood reserves are exercise, epinephrine, and hemorrhage. Therefore, in order to determine whether there are any blood reserves in normal subjects, the plasma volume, hematocrit reading, hemoglobin concentration, and serum protein concentration were determined before, during, and after: 1, exercise; 2, the administration of epinephrine; and 3, the loss of blood.

Method. All samples of blood were drawn without stasis. The plasma volume was measured by the dye method of Gibson and Evans¹⁷ using the photoelectric micro-colorimeter.¹⁸ A 1.6% solution of potassium oxalate was used as the anticoagulant for determining the hematocrit reading.¹⁷ The hemoglobin concentration in grams per 100 cc. was determined by the method of Evelyn.¹⁵ The serum protein concentration was calculated from the specific gravity of the serum as determined by the falling drop method of Kagan.²⁶ In 2 of the exercise experiments, the falling drop method was checked by the Kjeldahl method.

From the literature, it appears that in order to demonstrate the function

of the spleen as a blood reservoir, one must use either anesthetized or well-trained animals who have rested for some period of time before the experiment. In the experiments with exercise and the administration of epinephrine, laboratory workers who had no fear of the procedure served as subjects. Novocaine was used for local anesthesia. After the subject had rested quietly in bed for at least 30 minutes, a needle was inserted in an antecubital vein, and three samples of blood were taken for control determinations over a period of 15 minutes. When epinephrine was given, the needle was kept open by injecting a small amount of saline and was not removed until the experiment was completed. The needle was removed during the period of exercise.

Experiments. *Effect of Exercise in Normal and Splenectomized Subjects.* Observations were made on 6 normal and 2 splenectomized subjects. H. W. was an otherwise normal male who had had a splenectomy performed in 1918 for a benign tumor of the spleen. N. S. had had a splenectomy in 1927 because of repeated gastric hemorrhages associated with splenomegaly. He had had another hematemeses about 2 months before the experiment, and was slightly anemic.

Under basal conditions the plasma volume, hematocrit, hemoglobin, and serum protein values were first determined with the patient recumbent. As soon as the last sample was taken, exercise was begun on a bicycle ergometer. The normal subjects became exhausted in from 3 to 5 minutes. The splenectomized subjects did less work and did not exercise to the point of exhaustion. After exercise the subjects returned to the horizontal position and samples of blood were taken for determination of dye concentration, hematocrit, hemoglobin and serum protein values.

TABLE 1.—EFFECT OF EXERCISE ON THE HEMATOCRIT, HEMOGLOBIN, AND PROTEIN LEVELS OF NORMAL AND SPLENECTOMIZED SUBJECTS.

Subject.	Diagnosis.	Age (yrs.).	Wt. (kg.)	Basal plasma volume (cc.).	Relation to exercise.	Hemato- crit.	Hemo- globin (gm. per 100 cc.).	Serum protein (gm. per 100 cc.).
E. S.	Normal	32	85	2940	Before	44.9	14.7	6.5, 6.2*
					After	51.0	16.8	7.9, 7.7*
W. D.	Normal	31	74	3060	Before	41.9	14.4	5.9, 6.0*
					After	47.6	16.3	7.0, 7.1*
L. H.	Normal	27	77	3970	Before	43.0	14.6	6.3
					After	49.6	16.6	7.4
R. E.	Normal	27	67	2840	Before	41.7	13.4	6.4
					After	46.7	15.1	7.2
M. M.	Normal	24	75	2630	Before	48.3	15.9	6.6
					After	52.8	17.5	7.2
J. G.	Normal	43	72	2900	Before	44.2	14.4	6.3
					After	49.9	16.0	7.3
H. W.	Splenectomy	31	63	2470	Before	44.7	14.7	7.4
					After	47.2	15.3	7.9
N. S.	Splenectomy	22	68	4100	Before	35.7	10.6	6.5
					After	39.7	11.6	7.1

* Protein determinations were done by Kjeldahl method.

The results were similar in the normal and splenectomized subjects (Table 1). The concentration of the dye increased, indicating a decrease in plasma volume; the hematocrit, hemoglobin and serum

protein values increased. The amount that the plasma volume decreased could not be determined from the change in optical density of the dye-colored serum, because the optical density of dye-free serum increased after exercise.^{12b} The direction of the change in plasma volume could, however, be determined and it was clear that the plasma volume decreased and that no new plasma was added to the blood stream. If it is assumed that no protein enters or leaves the blood stream during exercise, the decrease in plasma volume can be calculated from the change in protein concentration. By this method the plasma volume decreased 220 to 590 cc. in the 6 normal subjects, and 160 and 340 cc. respectively in the 2 splenectomized subjects.

For a given increase in protein concentration, there was the same increase in hematocrit reading and hemoglobin concentration in both the normal and splenectomized subjects. As the normal subjects did more work, the absolute changes in protein, hematocrit, and hemoglobin were usually greater in the normal than in the splenectomized subjects. From the changes in protein concentration, hematocrit, and hemoglobin, which occurred after exercise, it was not possible to separate the splenectomized from the normal subjects. The data show that in both normal and splenectomized subjects, exercise caused a decrease in plasma volume, and that no demonstrable quantity of red cells was mobilized from the spleen.

Effect of Epinephrine in Normal and Splenectomized Subjects. Four normal and 2 splenectomized subjects were given 1 mg. of epinephrine subcutaneously immediately after the determination of the basal plasma volume, hematocrit, hemoglobin, and serum protein values (Table 2). The results were similar in both normal and splenectomized subjects. H. W. was the same subject referred to in the exercise experiment; M. S. had had a splenectomy in 1927 for thrombocytopenic purpura. Both subjects had been well since the operation. After 5 to 15 minutes, a rise in heart rate and systolic blood pressure occurred. The optical density of the dye-colored serum, hematocrit, hemoglobin, and serum protein levels increased. The amount that the plasma volume decreased cannot be determined from the change in the optical density of the dye-colored serum, because the optical density of the serum at times increased after the injection of epinephrine. The direction of the change in the plasma volume could, however, be determined and it was clear that the plasma volume did not increase, and that no new plasma was added to the blood stream. The slight rise in protein concentration suggested that there was a slight decrease in plasma volume. The changes in protein, hemoglobin, and hematocrit levels were small, but as they were in the same direction in every experiment, they were considered significant. As these changes occurred in both normal and splenectomized subjects, they cannot be attributed to the spleen. It was not possible to distinguish the

splenectomized from the normal subjects on the basis of the changes in protein, hemoglobin, and hematocrit values after the injection of epinephrine.

TABLE 2.—EFFECT OF THE SUBCUTANEOUS ADMINISTRATION OF EPINEPHRINE ON THE HEMATOCRIT, HEMOGLOBIN, AND PROTEIN LEVELS OF NORMAL AND SPLENECTOMIZED SUBJECTS.

(The resting values for hematocrit, hemoglobin and protein levels represent the average of three determinations.)

Subject.	Relation to injection of epinephrine.	Hematocrit reading.	Hemo-globin (gm. per 100 cc.).	Serum protein (gm. per 100 cc.).
E. G.	Before epinephrine	44.7	14.5	6.6
(normal)	5 min. after epinephrine	45.7	14.9	6.7
	10 " " "	46.5	15.2	6.8
	17 " " "	46.7	15.2	6.9
	26 " " "	46.1	15.2	7.0
D. C.	Before epinephrine	44.9	14.6	6.3
(normal)	5 min. after epinephrine	45.7	14.7	6.3
	10 " " "	45.7	14.9	6.7
	16 " " "	45.9	15.0	6.7
	26 " " "	46.6	15.2	6.6
	36 " " "	46.0	15.2	6.7
E. S.	Before epinephrine	42.8	14.2	6.7
(normal)	5 min. after epinephrine	45.0	14.6	6.8
	10 " " "	44.9	14.8	6.9
	21 " " "	44.6	14.9	6.9
	26 " " "	45.4	14.9	7.0
	31 " " "	45.0	14.9	7.0
	41 " " "	45.2	14.7	7.0
R. E.	Before epinephrine	41.8	13.8	6.4
(normal)	5 min. after epinephrine	43.1	14.1	6.5
	10 " " "	43.6	14.3	6.7
	15 " " "	43.5	14.0	6.6
	25 " " "	43.1	14.0	6.7
R. P.	Before epinephrine	43.2	13.6	7.0
(normal)	5 min. after epinephrine	44.9	14.3	7.2
	10 " " "	44.9	14.3	7.2
	15 " " "	44.7	14.0	7.2
	27 " " "	44.7	13.9	7.2
	33 " " "	45.0	13.8	7.1
H. W.	Before epinephrine	45.6	15.4	7.3
(splenectomized)	12 min. after epinephrine	46.4	15.5	7.4
	28 " " "	46.5	15.8	7.5
	31 " " "	47.2	15.8	7.5
	34 " " "	45.8	15.8	7.6
M. S.	Before epinephrine	44.6	14.2	6.8
(splenectomized)	5 min. after epinephrine	45.5	14.5	6.8
	10 " " "	45.7	14.7	7.0
	16 " " "	46.0	14.4	7.0
	26 " " "	45.0	14.2	7.1
	36 " " "	44.7	14.2	6.8

Effect in Normal Subjects of Hemorrhage and Tourniquets. In the dog, hemorrhage has been shown to cause contraction of the spleen, and may even cause a temporary rise in hematocrit reading if the hemorrhage is not too large.^{2,7} Reasoning from animal experiments and from teleologic considerations, hemorrhage should also be an effective means in man of mobilizing blood from any available reservoirs. In experiments previously reported,¹³ the plasma volume,

hematocrit value, and serum protein concentration of normal subjects were determined before and after the removal of 760 to 1220 cc. of blood. The hematocrit reading showed a steady decrease and at no time was there any evidence of red cells being poured into the circulation. During the first 2 hours after venesection, the plasma volume increased as protein-poor fluid was added to the circulation. There was no evidence of a reserve of plasma which was distinct from the circulating blood.

Blood was pooled in the limbs by applying tourniquets inflated to diastolic pressure to both upper thighs and one upper arm. In some cases sufficient blood was removed from the head and trunk to induce symptoms of collapse. Determination of the plasma volume and hematocrit level showed that in spite of the decreased quantity of blood in the trunk, no demonstrable number of red blood cells were added to the circulation.

Discussion. Although there is an abundance of evidence that the spleen serves as a reservoir of red cells in the dog, cat and horse,^{1,5,25,35a,b} there is little evidence that it has such a function in normal man. Dill, Talbott, and Edwards¹⁰ found that exercise caused a similar increase in hematocrit level and protein concentration in both normal and splenectomized subjects. Other workers³² found an increase in erythrocyte count in splenectomized as well as normal subjects after the administration of epinephrine, and concluded that this increase must be the result of hemoconcentration. After the injection of thorotrast, changes in size of the human spleen may be followed by Roentgen ray. Investigators^{31,37} using this technique have demonstrated that in man the injection of epinephrine causes only a slight decrease in the area of the normal spleen. If the spleen is enlarged, however, epinephrine may cause a marked decrease in size.³⁸

In the experiments reported here, the normal and splenectomized subjects showed similar changes in hemoglobin, hematocrit, and protein values after exercise and after administration of epinephrine. These changes, therefore, cannot be attributed to the spleen. In animals in which the spleen acts as an important reservoir of red cells, it is easy to distinguish between normal and splenectomized animals by comparing the hematocrit reading and hemoglobin concentration before and after exercise, or the administration of epinephrine. The fact that this method does not distinguish between normal and splenectomized human subjects indicates that in normal man the spleen is not important as a reservoir of red cells.

Experiments in which the carbon monoxide method of determining the blood volume was used have not produced conclusive evidence that the spleen acts as a reservoir of red cells in normal man. Chang and Harrop,⁹ measuring the blood volume by the carbon monoxide method, made observations on 6 subjects before and after exercise. In 3 experiments the change in carbon monoxide con-

centration in the blood was so slight that it was within the experimental error; in 3 cases a just appreciable although definite decrease in carbon monoxide concentration was observed. They interpreted this as due to either a slight diffusion of gas into the muscle hemoglobin or to the addition of a small quantity of red cells to the circulation from the spleen or other reserves. Yang and Chang¹⁰ stated later that, in the time that was allowed for mixing, carbon monoxide diffused evenly through blood in the human spleen. It is possible that the slight decrease in carbon monoxide concentration with exercise (indicating a higher blood volume) resulted from diffusion of some of the carbon monoxide into the muscle hemoglobin.

Barcroft,⁴ working with the carbon monoxide method and using an adequate rebreathing time, found an increase in blood volume when human subjects were placed in a warm room. He found little change in hemoglobin concentration. Therefore, an increase in both the red cell volume and plasma volume would have had to occur. As the time was too brief for the formation of new red cells, the increase in red cell volume would have had to be due to the addition of red cells to the circulation from some blood reservoir, such as the spleen. Bazett and his coworkers,⁶ using the carbon monoxide method, found a decrease in red cell volume when human subjects were changed from a room maintained at a constant warm temperature to a cool room. In view of the evidence presented by Yang and Chang¹⁰ that in man carbon monoxide mixes with the blood of the spleen if an adequate mixing time is allowed, it is difficult to explain these changes in red cell volume as due to release or storage of red cells in the spleen. A possible explanation may be that a greater quantity of carbon monoxide combines with muscle hemoglobin in a warm environment than in a cool environment. To offer a definite answer to this question, it would be necessary to compare the effect of environmental temperature on splenectomized and normal subjects.

It has been shown that in certain animals other than man, the spleen is not an important reservoir of red blood cells. In the guinea-pig and rabbit, as contrasted with the dog, there is only slight contraction of the spleen and relatively little increase in the hematocrit after the administration of epinephrine.²¹ The efficiency of the spleen as a storehouse for red blood cells can be correlated with the amount of muscular tissue in the spleen. The spleens of the dog, cat and horse have large amounts of smooth muscle, while the spleens of the rat, rabbit and man are poor in smooth muscle.²³

Although the evidence indicates that under normal conditions in man the spleen does not serve as an important reservoir of red cells, there is considerable evidence that under certain pathologic conditions in which the spleen is enlarged, it may fulfill this function. This is particularly true in hemolytic jaundice where a marked increase in hematocrit reading and erythrocyte count may occur

after the subcutaneous injection of epinephrine. This effect does not occur after splenectomy.³⁸

Using the older dye methods for determining plasma volume, many investigators found an increase in plasma volume rather than a decrease after exercise.^{8,36,39} Workers using the dye method with an adequate mixing time have consistently found that the plasma volume decreased after exercise.^{19,27} The older dye methods gave an increased plasma volume after any stimulus which caused an increase in the velocity of the circulation, such as epinephrine, breathing of carbon dioxide, and heat.^{33,39} Since these changes in plasma volume were not accompanied by corresponding changes in the hematocrit, it was believed that the red cell volume was also increased. Because of the apparent increase in volume after these various stimuli, the total blood volume obtained at rest was designated as the circulating blood volume and the increase in volume after exercise was thought to be the result of the mobilization of blood from various blood reservoirs.

The older dye methods allowed only a short time between the administration of the dye and the withdrawal of the sample of blood for the determination of dye concentration. It has been shown that complete mixing of the dye in the blood stream may not occur in this period of time.³¹ Gibson and Evans¹⁷ pointed out that the mixing time in different subjects varied, and that the average mixing time for normal subjects was 7.5 minutes. With a short circulation time the mixing was rapid; as the circulation time increased the mixing time became more prolonged. It thus appears that what was designated as the circulating blood volume was a falsely low volume because of the allowance of inadequate time for complete mixing of the dye throughout the plasma, and that the change after exercise which was designated as release of blood from blood reservoirs, was only a decrease in dye concentration due to more adequate mixing of the dye.

In the use of the carbon monoxide method, similar errors have been made. Douglas¹¹ pointed out that the period of rebreathing used by Haldane and Smith²⁰ in their original method was too short and gave a falsely low volume. The striking increase in volume after exercise and heat described by Eppinger and Schürmeyer¹⁴ was probably the result of using too short a period of rebreathing. Chang and Harrop⁹ have shown that as long as 15 minutes of rebreathing is required before a constant concentration of carbon monoxide is obtained in the blood.

The evidence seems to indicate that in the normal human subject there is no place in the body where a measurable quantity of blood lies in non-circulating pools or reservoirs. It is true that all blood is not moving at the same speed and that when a dye or carbon monoxide is added to the blood stream, it is first mixed and shows the highest concentration in the parts of the blood stream that are

flowing more rapidly. It is possible that in part the dye mixes slowly because the central portion of the stream in the small vessels moves more rapidly than does the peripheral portion. This is probably not the main factor because the carbon monoxide mixing time is at least as long as the dye mixing time, and the carbon monoxide is carried by the red cells which move in the axial portion of the stream.

As it has been demonstrated that only about 16% of the blood volume as measured by the dye and hematocrit method is present in one upper and both lower limbs,^{12a} it is evident that at rest the majority of the blood must be in the abdominal and thoracic cavity. It is also clear that under certain conditions, such as hemorrhage, this blood can be redistributed. It has been pointed out²⁸ that the portal system, with its two sets of resistances, probably plays a large part in the adjustments which occur when the vascular bed of the muscles is dilated, or when the blood volume is decreased by hemorrhage or loss of fluid. It is probable that in the resting state blood flows slowly through portions of the splanchnic area, and that when blood is needed in other parts of the body, as after hemorrhage, the small vessels contract, diminishing the size of the vascular bed and furnishing more blood for other portions of the circulation. This is a redistribution of the circulating blood and not the addition of non-circulating blood to the vascular bed.

Summary. 1. Exercise caused a decrease in plasma volume and an increase in hematocrit, hemoglobin and serum protein values in both normal and splenectomized subjects. For a given increase in protein concentration, the same increase in hematocrit reading occurred in both normal and splenectomized subjects.

2. Epinephrine produced an increase in hemoglobin, hematocrit, and serum protein levels in both normal and splenectomized subjects.

3. In normal subjects attempts to demonstrate reserves of red cells or of plasma by removing large quantities of blood were unsuccessful. Pooling of blood in the extremities did not cause a demonstrable discharge of red cells into the circulation.

4. A review of the literature shows that technical errors account for the large increases in blood volume which have been described in normal subjects after stimuli, such as epinephrine or exercise, which increase the velocity of the circulation.

5. Although there is an abundance of evidence that the spleen serves as a reservoir of red blood cells in the dog, cat and horse, the evidence presented here indicates that blood reservoirs of this nature do not exist in normal human subjects.

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**THE EFFECT OF ARTERIAL AND VENOUS CONSTRICTION
INDUCED BY PAREDRINE (p-HYDROXY- α -METHYL-
PHENYLETHYLAMINE HYDROBROMIDE) ON THE
LUNG CAPACITY AND ITS SUBDIVISIONS.***

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EARLIER work from this laboratory^{4b,21a,b} has shown that parendrine,¹ a sympathomimetic amine, causes marked constriction of the peripheral arteries and veins, resulting in increased systemic arterial and venous pressures. Data obtained from studies on the effects of parendrine show that the administration of that drug

* This study was aided by a grant from Smith, Kline & French Laboratories, Philadelphia.

induces hypertension which resembles essential hypertension: in both there is generalized arteriolar constriction without changes in skin temperature, oxygen consumption or cardiac minute volume output.^{1,4b,15} It has been suggested²⁹ that the peripheral vasoconstriction of essential hypertension may increase the blood content of the lungs. The question therefore arises as to whether or not this marked widespread vasoconstriction similarly causes redistribution of the circulating blood. In an attempt to gain information on the effect of the administration of paredrine on the pulmonary blood content, we have made measurements of the pulmonary air capacity and its subdivisions; direct measurement of pulmonary blood volume in man is not possible. Information bearing on this point is essential for a complete understanding of the action of this drug if it is to be used therapeutically; its use has already been suggested in conditions in which it is desirable to raise the blood pressure without increasing the cardiac output directly.^{3,4b,23} Many of the properties of paredrine are useful for the present study: its vasoconstricting action is prolonged, it does not cause restlessness or other untoward symptoms, and it is not a bronchodilator.

Methods. Five normal subjects were used, ranging in age from 23 to 35. Measurements were made with the subject in supine position, arms at side, with one small pillow beneath the head. The determinations on Subjects 1, 2, 3, and 4 were made several hours after the last meal, and were preceded by a rest period of 20 minutes. Subject 5 was in the basal, postabsorptive state. Paredrine hydrobromide was given orally in solution, and measurements were made at the peak of the pressor action, usually 15 to 45 minutes after administration. The closed circuit method of Christie¹⁰ was used to determine the functional residual air, which, in that author's terminology, is the air contained in the lungs at the end of normal expiration. The bell type spirometer used in these studies had a capacity of 6 liters, and a dead space, including the mouthpiece, of 1270 cc. A carbon dioxide absorber of the type described by Waters²⁸ containing 475 gm. of Wilson's Soda Lime, 4-8 mesh, was used in the circuit, and the carbon dioxide content of the air at the end of the experiment was less than 0.4%. Approximately 5 liters of oxygen were added to the spirometer at the start of the experiment. Gas analysis was performed in duplicate, using a Haldane apparatus with a burette calibrated to permit the direct determination of nitrogen in concentrations ranging from 27% to 74%. In the calculation of functional residual air a correction of 100 cc. for nitrogen excretion in a 7-minute test period was used in the modified formula proposed by Hurtado *et al.*²⁰ and the result was corrected to give volume at 37° C. The rate of oxygen consumption and the respiratory minute volume were determined from the graphic record of the respiration. At the conclusion of the determination, reserve and complementary air were determined separately by measurement on the graphic record of excursions from the resting expiratory level after forced expiration and forced inspiration. Vital capacity was determined separately, using a larger spirometer.

Critique of Method. The small volume closed circuit method for determining residual air has been criticized by Lassen and coworkers,²⁴ and these authors¹² as well as others¹⁷ have suggested methods to overcome these objections. However, Kaltreider, Fray and Hyde²² concluded that the error in measurements made by Christie's

method was small. The newer methods are much more complicated, involving either addition of gases to a system at a constant rate or taking repeated alveolar air samples. Christie's method is much simpler, involving a minimum of coöperation on the part of the patient, and has been found reasonably accurate by most observers in normal subjects who do not have an unusually high mid-capacity.^{11,17,22,24} Even if a small error occurs in the absolute values obtained, it is felt that the comparative data are valid for the purposes of this study.

The correction of 100 cc. for nitrogen excretion is slightly higher than that originally suggested by Christie. Recent studies by Behnke *et al.*⁷ and Richards and coworkers¹³ of the elimination of nitrogen through the lung during quiet breathing of 100% oxygen show that approximately 220 cc. of nitrogen is eliminated in 7 minutes in an average normal subject. In our experiments, the nitrogen concentration of the expired air at the termination of the test period was usually 40% to 45%; this represents a decrease of slightly less than 50% from the original value of 79%. Since nitrogen excretion is said to obey the usual gas laws, we have used slightly less than half of the value obtained when pure oxygen is breathed. This can be only an average value, since it will vary with the cardiac output and final nitrogen concentration in each subject tested, but variations from the average figure large enough to impair seriously the accuracy of the determination are improbable. It should be noted that errors due to this factor will not impair the validity of the present study, since results obtained before and after the use of a drug are compared.

Results. Doses of paredrine sufficient to cause marked changes in blood pressure produced no significant change in ventilation, oxygen consumption, total pulmonary capacity or any of its subdivisions (Table 1).

Discussion. The relation between changes in blood content of the lungs and variations in their pulmonary air capacity has been appreciated for many years. It has been suggested that changes in pulmonary capacity and its subdivisions resulting from variations in posture are due to redistribution of the blood in the body,^{5,8,16} but this concept is still controversial.^{18,25} A clear-cut and familiar instance of change in the subdivisions of the pulmonary capacity secondary to increased blood content is afforded by chronic congestive failure.² It has also been shown that a very rapid intravenous infusion (*i. e.*, 1500 cc. in 12 minutes) of physiologic saline solution may decrease the vital capacity in man by as much as 30%.⁴ Conversely, increased vital capacity due to diminished blood content of the lungs has been produced experimentally in man by measures which promote pooling of blood in the extremities^{5,9c} and by venesection.^{9a} The subdivisions of the pulmonary capacity in man can therefore be influenced by various measures which appear to depend on a change in the blood content of the lung.

TABLE 1.—THE EFFECT OF PAREDRINE ON LUNG CAPACITY AND ITS SUBDIVISIONS.

No	Date.	Age.	Sex.	Body surface, sq. m.	Dose.	B.P.	O ₂ cons., cc./min.	Normal O ₂ cons., cc./min.	BMR., %.	Resp. min. vol., liters.	Functional residual air, liters.	Reserve air, liters.	Residual air (12-13), liters.	Vital capacity, liters.	Total capacity (14-15), liters.	Comple- ment air, liters.
1. W. MeB.	5/27	28	M	1.81	Cont.	88/60	273	247	+11	8.2 9.5	2.3 2.2	3.7	5.4	2.6
	6/3	Cont.	88/60	267	247	+ 8	8.0	2.0	0.56	1.7	3.7	5.4	2.6
	6/3	40 mg.	120/90	256	247	+ 2	8.4	2.4	0.56	1.8	3.7	5.5	2.6
	6/26	Cont.	88/60	242	247	+ 4	7.5	2.2	0.56	1.6	3.7	5.3	2.6
2. M. D. A.	6/28	40 mg.	120/80	256	247	+ 4	8.4	2.3	0.56	1.7	3.7	5.4	2.6
	5/29	35	M	1.72	Cont.	..	250	235	+ 6	4.8 5.3	2.0 1.9	0.56	1.4 1.3	4.2	5.6	3.5
	6/4	Cont.	114/68	246	235	+ 5	4.7	1.8	0.56	1.2	4.2	5.5	3.5
	6/4	40 mg.	150/84	250	235	+ 6	4.6 4.4	1.8 1.9	0.60	1.3 1.3	4.2	5.5	3.6
3. V. I.	6/16	28	F	1.54	Cont.	124/68	244	197	+24	5.6 5.4	2.3 2.4	0.84	1.5 1.5	3.7	5.2	2.7
	6/16	Pared. 30 mg.	190/100	248	197	+26	7.7 4.7	2.4 2.1	0.72	1.7 1.4	3.7	5.4	2.7
	6/20	23	M	1.96	Cont.	108/60	285	267	+ 7	7.5	3.7	1.00	2.7	5.3	8.4	3.8
4. N. Z.	6/20	Pared. 30 mg.	166/100	270	267	+ 1	6.5 7.2	3.5 3.3	1.00	2.5 2.3	5.3	8.2	3.9
	6/27	35	M	1.84	Cont.	104/70	209	251	-19	8.8 8.0	2.3 1.9	0.76	1.5 1.2	3.7	5.0	2.8
5. S. T.	6/27	30 mg.	138/96	219	251	-13	7.0 6.2	2.1 2.0	0.64	1.5 1.3	3.7	5.2	3.0
	6/28	40 mg.	156/100	227	251	- 9	11.0 8.3	2.0 2.1	0.60	1.5 1.5	3.7	5.2	2.8

Experiments in animals also show that the blood content of the lung may be influenced by various measures. Sjöstrand has reviewed this subject and also presents data from his own experiments.²⁶ He found that many measures, such as excitement, asphyxia, and drugs change the amount of blood which may be found in the lungs of small animals killed suddenly. Drinker, Peabody, and Blumgart¹⁴ found that the lungs of cats are capable of large changes in blood content under experimental conditions, and that these changes are reflected in changes in respiration.

Only a small number of studies on the effect of sympathomimetic drugs on the pulmonary subdivisions in man have been recorded. Budelmann^{9b} reported that adrenalin decreases the vital capacity. Hurtado and Kaltreider,¹⁹ however, found adrenalin exerts no significant effect on subdivisions of the pulmonary volume in an asthmatic subject studied between attacks, although it produces marked changes during an attack. Sympatol, which resembles paredrine in its pharmacologic action, may increase or decrease vital capacity in normal subjects;^{9b} veritol (p-hydroxy- α -N-dimethylphenethylamine sulphate), which resembles paredrine even more closely, is said to increase it.⁶ The paucity of data on the effect of sympathomimetic drugs, especially in regard to subdivisions of the pulmonary air capacity, other than the vital capacity, makes general conclusions impossible. Nevertheless, it is worthy of emphasis that the only thorough studies of the effects of these substances on all the subdivisions of the lung volume are in agreement: neither the total lung volume nor any of its subdivisions is changed by the action of such drugs.

There is little doubt that changes in the blood content of the lungs may occur in animals and man, and that such changes can determine variations in the respiratory subdivisions. The volume of blood in the capillaries is the important factor in this regard. These vessels make up a great part of the alveolar wall; accordingly changes in the air capacity of the lungs reflect changes in the volume of the pulmonary capillary bed as a whole. The absence of changes in the subdivisions of the pulmonary capacity after administration of paredrine suggests that the capillary blood content of the lung is not markedly influenced by this drug; pulmonary congestion is not produced. The fact that the administration of paredrine causes no change in respiratory dynamics is in harmony with this conclusion. Additional evidence in this regard is afforded by the results of earlier studies from this laboratory.^{4b} Stewart²⁷ called attention to the fact that the amount of blood in the lungs may be calculated if the cardiac output and pulmonary circulation time are known. Since neither of these two measurements changes after the administration of paredrine,^{4b} it is clear that no change in pulmonary blood volume occurs either.

Summary and Conclusions. 1. The subdivisions of the pulmonary volume were measured in seven experiments on 5 normal subjects after the administration of paredrine.

2. No significant deviation from the control values occurred.

3. Paredrine therefore does not produce marked changes in the blood content of the capillaries of the lungs.

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THE COMPARATIVE VALUE OF ETHER AND PARALDEHYDE AS AGENTS FOR MEASUREMENT OF THE ARM TO LUNG CIRCULATION TIME IN 50 PATIENTS WITH AND 50 PATIENTS WITHOUT HEART FAILURE.

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MEASUREMENT of the circulation time of the blood is acquiring increasing importance as a test in the study of heart failure and other diseases affecting the velocity of blood flow. In practice, the term "circulation time" indicates the time elapsing between

the injection of a drug into one of the peripheral veins and the perception of a sensation produced by the drug at a distant point in the patient's body. The term is further modified by designating the point of injection (usually a vein in the antecubital fossa) and the point of perception. Any condition which slows the velocity of blood flow usually causes prolongation of the circulation time; any condition which increases the velocity of blood flow has the effect of shortening the circulation time. This accounts for the usefulness of the test in heart failure, acute and chronic cardiac compression, venous obstruction, myxedema, and polycythemia vera, in all of which the circulation time tends to be prolonged, and in hyperthyroidism in which the circulation time often is shorter than normal.

In clinical practice, two groups of drugs are employed for estimation of the circulation time. One group has as the point of perception the bronchopulmonary or olfactory epithelium, so that the drug traverses a pathway from an antecubital vein through the systemic veins, the right auricle, the right ventricle, and the pulmonary arteries to the pulmonary capillaries. This is called the arm to lung circulation time, pulmonary circulation time, or right heart time. In cases of heart failure, the arm to lung circulation time is essentially an appraisal of the efficiency of the right ventricle. The drugs commonly used for this measurement are ether and paraldehyde. The end point of the test with ether is the appreciation of the odor of the drug by the patient (*subjective end point*) or by the operator (*objective end point*). The end point with paraldehyde is a sharp paroxysm of coughing produced by the irritating effect of the drug on the bronchopulmonary epithelium or appreciation of the odor of the drug on the patient's breath by the operator (*objective end points*) or perception of the odor of the drug by the patient himself (*subjective end point*).

The second group of drugs used for measuring the circulation time has as the place of perception some point supplied by the peripheral arteries of the head and neck. The pathway of the drug includes that traversed by the drugs used for determination of the arm to lung circulation time and, in addition, the pulmonary veins, left auricle, left ventricle, and systemic arteries. In this group of drugs are calcium gluconate and magnesium sulphate which produce a sensation of warmth in the throat and tongue, saccharin which gives a sweet taste, decholin which gives a bitter taste, sodium cyanide which causes a gasp when it reaches the carotid sinus, and *lobelin which causes coughing when it reaches the carotid sinus*. These drugs, therefore, are used variously for the arm to tongue circulation time or arm to carotid sinus circulation time. Other terms describing the measurements obtained with these drugs are the arm to head circulation time and total circulation time. This time normally varies from 9 to 16 seconds. In cases of heart

failure, measurement of the total circulation time affords a means for appraisal of the efficiency of the whole heart and, when considered in relation to the arm to lung circulation time, gives in addition an evaluation of the efficiency of the left ventricle in particular.

The lung to tongue circulation time is computed by subtracting the arm to lung from the arm to tongue circulation time. Its accurate computation is said to be important, particularly in cases of isolated right ventricular failure in which it remains within normal limits of from 5 to 10 seconds, although the arm to tongue and arm to lung circulation times are prolonged.⁵

In the course of performing various circulation tests on patients with heart failure, one of us found³ that paraldehyde sometimes gave outlandish results for the arm to lung circulation time, and that ether was for the most part a more reliable agent. Our present study had its inception therefore in an occasional casual observation of the apparent inaccuracy of the arm to lung circulation time as measured by means of paraldehyde. Candel¹ and Manchester⁴ independently have discussed the value of paraldehyde as a means for determination of the arm to lung time. Both authors found this drug to give results comparable to those obtained with ether in patients with normal circulation times and emphasized the advantage which accrues to the use of paraldehyde instead of ether because of the objectivity of the end point of the former drug. It has been our interest to endeavor to compare the relative accuracy of these two agents for measurement of the arm to lung circulation time in patients with various degrees of congestive heart failure. The arm to lung circulation time has been determined by means of ether and paraldehyde, used separately but almost simultaneously, in 50 patients with congestive heart failure and in 50 other patients without heart failure, who served as controls. In the latter group are included a number of patients having etiologic factors for heart disease but in no case was there demonstrable evidence of heart failure at the time the studies were performed.

Technique.—Estimation of the arm to lung circulation time was made in every case after the patient had been resting in bed for at least $\frac{1}{2}$ hour. At the time of the test the patient was placed in the supine position with the arm used, abducted through an angle of about 45 degrees and in such position that the veins of the antecubital fossa were at or only slightly below the level of the right auricle. A syringe containing a mixture of 5 minims of fresh ether with 10 minims of sterile physiologic salt solution was used first. After entering an antecubital vein with a 19- or 20-gauge needle, about 30 seconds was allowed to elapse after removal of the tourniquet, in order to permit restoration of the flow of venous blood. Then the ether-saline mixture was injected *as rapidly as possible* into the vein. A stop watch was started by an assistant at the beginning of the injection and two measurements were made, using both the objective and subjective end points for ether. An important duty of the assistant or the operator consisted in endeavoring to detect the odor of the drug at the patient's nose. When the patient could no longer detect an odor of ether, 1.4 cc. of fresh

paraldehyde was injected *as rapidly as possible* through the needle, which had remained undisturbed in the vein. Again the stop watch was started at the beginning of the injection, and an attempt was made to record three end points for the reaction to paraldehyde in each case. These end points were the perception of an odor of paraldehyde by the patient, similar perception by the operator, and a paroxysm of coughing. In normal person the arm to lung time measured with ether has been reported to vary between 3.5 and 8 seconds;² with paraldehyde, between 3 and 9.5 seconds. Candel postulated 11 seconds as the upper limit of the normal value for the arm to lung time, measured with paraldehyde.

TABLE 1.—CASES WITHOUT HEART FAILURE.

Arm to lung circulation time (seconds).*

Case No.	Diagnosis.	Ether.	Paraldehyde.	Difference (paraldehyde minus ether).
1	Bronchiectasis	8.0	8.4	0.4
2	Hypertension	8.0	9.8	1.8
3	Pneumonia	(S)8.0	8.4	0.4
4	Gastric cancer	(O)7.0	7.0	0.0
5	Hypertension	4.0	7.8	3.8
6	Hypertension	5.0	6.5	1.5
7	Hypertension	6.0	10.0	4.0
8	Arteriosclerosis	(O)5.6	10.8	5.2
9	Cerebral apoplexy	(O)8.4	8.2	-0.2
10	Bronchiectasis	(O)8.0	(O)8.0	0.0
11	Hypertension	5.8	7.8	2.0
12	Banti's syndrome	5.6	5.8	0.2
13	Nephritis	4.8	4.8	0.0
14	Hypertension	(S)6.8	7.0	0.2
15	Hypertension	7.6	8.2	0.6
16	Tuberculosis	9.0	8.4	-0.6
17	Cardiac neurosis	5.0	5.0	0.0
18	Tuberculosis	6.0	6.4	0.4
19	Lung abscess	7.0	7.2	0.2
20	Epilepsy	5.0	6.2	1.2
21	Coronary arteriosclerosis	(O)7.0	9.0	2.0
22	Hypertension	(O)6.0	6.2	0.2
23	Hypertension	(S)7.4	11.0	3.6
24	Hypertension	7.0	9.8	2.8
25	Hypertension	(S)5.4	10.0	4.6
26	Tuberculosis	6.0	6.8	0.8
27	Alcoholism	(O)7.0	7.2	0.2
28	Bronchiectasis	8.2	9.0	0.8
29	Cerebral apoplexy	9.0	9.2	0.2
30	Hypertension	(O)8.4	8.6	0.2
31	Hypertension	(O)9.4	10.0	0.6
32	Hematemesis	(S)7.0	7.4	0.4
33	Brain tumor	(S)6.4	6.8	0.4
34	Tabes dorsalis	8.0	8.4	0.4
35	Hypertension	6.2	7.2	1.0
36	Pleurisy	7.6	7.8	0.2
37	Lung abscess	8.0	8.4	0.4
38	Cerebral vascular syphilis	5.0	5.2	0.2
39	Cirrhosis of liver	(S)7.6	8.0	0.4
40	Rheumatoid arthritis	4.8	5.4	0.6
41	Bronchial asthma	(S)4.0	(S)8.0	4.0
42	Ventricular tachycardia	8.8	10.6	1.8
43	Neurosis	8.6	9.0	0.4
44	Tuberculosis	(S)6.6	6.8	0.2
45	Peptic ulcer	(S)7.4	8.0	0.6
46	Bronchial asthma	7.4	9.4	2.0
47	Bronchiectasis	8.6	9.6	1.0
48	Hypertension	5.0	8.0	3.0
49	Pneumonia	9.0	8.8	-0.2
50	Bronchial asthma	8.0	(O)8.0	0.0

* (O) indicates that the end point of the time recorded was the perception of the odor of the drug by the operator. (S) indicates that the end point was the perception of the odor by the patient. The absence of any indicating letter before the time recorded for ether means that the subjective and objective end points were obtained simultaneously. The absence of any indicating letter before the time recorded for paraldehyde means that the end point was a paroxysm of coughing.

Clinical Results. The results obtained for measurement of the arm to lung circulation times by means of ether and paraldehyde in the 50 control cases are shown in Table 1; those for the 50 cases of heart failure are shown in Table 2. In the tables, the lowest value for the circulation time is the one recorded. For example, in some cases the subjective end point for ether is obtained sooner than the objective end point, and *vice versa*. Similarly, it occasionally happens that the odor of paraldehyde is perceived several

TABLE 2.—CASES WITH HEART FAILURE.

Case No.	Etiologic type of heart disease.	Arm to lung circulation time (seconds).*		
		Ether.	Paraldehyde.	Difference (paraldehyde minus ether).
1	Rheumatic	12.6	16.4	3.8
2	Arteriosclerotic	21.0	28.2	7.2
3	Hypertensive	19.4	29.0	9.6
4	Rheumatic	12.2	21.0	8.8
5	Rheumatic	(O)15.0	18.0	3.0
6	Hypertensive	12.6	25.0	12.4
7	Hypertensive	14.8	18.4	3.6
8	Rheumatic	42.0	No end point	
9	Hypertensive	13.4	9.6	-3.8
10	Hypertensive	9.4	(S)(O)9.4	0.0
11	Hypertensive	(O)17.0	13.0	-4.0
12	Rheumatic	(O) 8.6	15.0	6.4
13	Arteriosclerotic	10.0	13.6	3.6
14	Hypertensive	9.0	11.0	2.0
15	Beriberi	(O)21.0	(S)41.0	20.0
16	Hypertensive	(O)14.6	24.2	9.6
17	Hypertensive	27.0	No end point	
18	Hypertensive	(O) 8.8	15.0	6.2
19	Hypertensive	11.0	8.0	-3.0
20	Syphilitic	22.4	42.6	20.2
21	Hypertensive	11.6	12.4	0.8
22	Arteriosclerotic	(S)13.0	12.0	0.0
23	Syphilitic	32.0	No end point	
24	Syphilitic	17.0	(S)19.0	2.0
25	Arteriosclerotic	10.0	16.8	6.8
26	Hypertensive	14.0	(S)(O)20.0	6.0
27	Hypertensive	10.6	14.4	3.8
28	Hypertensive	11.0	13.0	2.0
29	Hypertensive	20.0	22.0	2.0
30	Hypertensive	(O)10.0	(S)24.0	14.0
31	Arteriosclerotic	(S)11.4	15.0	4.6
32	Hypertensive	(O)14.0	19.4	5.4
33	Arteriosclerotic	16.6	21.4	4.8
34	Hypertensive	11.0	9.6	-1.4
35	Syphilitic	(O)13.0	17.0	4.0
36	Syphilitic	12.0	(S)15.0	2.8
37	Hypertensive	11.0	15.0	4.0
38	Syphilitic	15.0	21.0	6.0
39	Hypertensive	(O)11.0	9.4	-1.6
40	Hypertensive	12.0	10.0	-2.0
41	Hypertensive	(S)20.0	21.0	1.0
42	Hypertensive	(O)11.2	16.0	4.8
43	Rheumatic	(O)15.0	18.0	3.0
44	Syphilitic	(O)10.0	12.0	2.0
45	Rheumatic	15.0	18.0	3.0
46	Syphilitic	11.0	15.2	4.2
47	Hypertensive	(S)10.6	14.8	4.2
48	Hypertensive	(S)11.0	18.0	7.0
49	Hypertensive	(O) 9.0	12.0	3.0
50	Arteriosclerotic	(O)11.0	14.0	3.0

* (O) indicates that the end point of the time recorded was the perception of the odor of the drug by the operator. (S) indicates that the end point was the perception of the odor by the patient. The absence of any indicating letter before the time recorded for ether means that the subjective and objective end points were obtained simultaneously. The absence of any indicating letter before the time recorded for paraldehyde means that the end point was a paroxysm of coughing.

seconds before the patient coughs, although the paroxysm of coughing and the odor of the drug usually appear simultaneously.

In the control cases, there was no instance in which there was complete failure to obtain an end point with ether and paraldehyde. There was 1 case in which the patient had no sense of smell, and the end points for both drugs were objective. There was another case in which the patient did not notice the odor of paraldehyde, and there were 2 cases in which paraldehyde failed to provoke coughing, but in these 3 cases the odor of the drug was easily detected objectively by the operator.

Forty two (84%) of the 50 control cases had a shorter arm to lung circulation time when measured with ether than with paraldehyde. The difference in seconds varied from 0.2 to 5.2. In almost all cases, however, the difference was insignificant for practical purposes. Furthermore, in all cases the circulation time measurements with both drugs were within the limits established as normal by other workers. There were 5 cases (10%) in which the values were identical for the two measurements. In the remaining 3 cases (6%) the values obtained with paraldehyde were shorter by from 0.2 to 0.6 second than those with ether, again an insignificant difference.

Very few unpleasant reactions were noted as the result of administering either ether or paraldehyde to the control cases. In 3 cases, paraldehyde caused slight drowsiness and in 1 case, transient headache. The odor of paraldehyde tended to persist longer than that of ether, and in many cases was objectionable to the patient for as long as 10 minutes. In 1 case, ether caused severe pain along the course of the vein into which it was injected. The pain lasted about 24 hours, but there was no objective evidence of phlebitis.

In the cases of heart failure, there were no instances in which the use of ether for measuring the circulation time was a complete failure. In 2 cases, the patient did not smell the drug, but the operator was able to record its presence. Using paraldehyde, there were 3 cases in which no end point to the reaction could be obtained. In these cases, the circulation time, as measured with ether, was more prolonged than in any others of the group. There were 3 other cases in which paraldehyde failed to induce coughing, although the odor of the drug could be detected either by the patient or by the operator. Thus, there were 6 cases in all in which paraldehyde did not produce coughing. This should serve to emphasize that a paroxysm of coughing is not necessarily the most reliable end point for the reaction with paraldehyde. An attempt should always be made both by the patient and by the operator to obtain the odor of the drug.

There were 39 cases (76%) of heart failure in which the circulation time measured by means of ether was shorter than that measured by means of paraldehyde. The differences of the two measure-

ments ranged from 0.8 to 20.2 seconds, with an average difference of 5.76 seconds. There were 29 cases (58%) in which the difference was greater than 3 seconds and therefore certainly significant. There were 3 additional cases (6%) in which no difference could be computed because an end point was not obtained with paraldehyde. In 2 cases (4%) the circulation time was the same with each drug. In 6 cases (12%) the circulation time with paraldehyde was shorter than that obtained by means of ether. Differences in these cases ranged from 1.4 to 4 seconds and were greater than 3 seconds in only 2 cases.

Unpleasant side reactions with ether and paraldehyde were a little more common in the patients with heart failure than in the control group. Drowsiness after injection of paraldehyde was observed in 7 cases. Again, the odor of paraldehyde was disagreeable in many instances because of the length of time it persisted. In 8 cases, ether provoked transient but objectionable pain.

Discussion. It is obvious from our study that the records obtained for the arm to lung circulation time with paraldehyde are approximately the same as those obtained with ether in subjects who have no cause for slowing of the velocity of blood flow. However, in the majority of cases of heart failure the records obtained with paraldehyde are significantly longer than those obtained with ether. Moreover, the differences in circulation time measured with these two drugs are by no means constant and bear no absolute relation to the duration of the circulation time. These facts indicate that ether is a more reliable agent for accurate measurement of the arm to lung circulation time. It is true that the use of paraldehyde will demonstrate the presence of a slowed circulation rate such as occurs in heart failure. However, paraldehyde gives a less exact appraisal of the severity of heart failure, and probably could not be depended upon for the type of accurate measurements that are occasionally needed in the diagnosis of isolated right ventricular failure, in which a knowledge of the lung to tongue circulation time is of considerable importance.⁵

It is presumed that the reaction produced as an end point by any drug used for measurement of the circulation time depends upon the arrival at the point of perception of an adequate concentration of the drug. Therefore, in any case in which the concentration of the drug is inadequate, no end point for the circulation time can be obtained, or in cases in which the concentration is only partially adequate, a delayed reaction may result. It seems likely that in cases in which the velocity of the circulation is slowed, paraldehyde usually fails to reach the point of perception in sufficient concentration. Possibly, the use of larger doses than those originally recommended for paraldehyde would give more reliable results, but unpleasant side effects probably would be more frequent and more severe. The inferiority of paraldehyde as compared to ether

may have its basis in two factors. Paraldehyde is less volatile and consequently must diffuse more slowly from the pulmonary capillaries into the air passages of the lungs. Further, paraldehyde is less miscible with blood than ether, and consequently would be carried along in the blood stream less rapidly.

Summary and Conclusions. 1. Measurement of the circulation time is useful in the diagnosis and study of a number of diseases, and especially of heart failure.

2. A comparison of the relative value of ether and paraldehyde for measurement of the arm to lung circulation time is presented. These two drugs have already been reported to give approximately equal results in normal persons. This has been confirmed in our studies in 50 patients having no cause for delay of the circulation time.

3. Comparison of circulation time measurements obtained almost simultaneously by means of ether and paraldehyde in each of 50 patients with heart failure show that measurements with paraldehyde are usually significantly longer than those with ether. Such differences constitute an inaccuracy which may be misleading clinically.

4. Speculation as to the possible reasons for the discrepancy in measurements made with ether and paraldehyde is offered, and the conclusion drawn that ether is the agent of choice for estimation of the arm to lung circulation time.

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THE CHARACTERISTIC ELECTROCARDIOGRAMS IN LEFT VENTRICULAR STRAIN WITH AND WITHOUT AXIS DEVIATION.*

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THE characteristic alterations in electrocardiograms of patients with primary left ventricular strain have been previously discussed in the literature.^{1,2,6,12,13,17,19,22,24} The typical forms with axis deviation are definitely established, but there has been too little discus-

* Aided by the A. D. Nast Fund for Cardiac Research and the A. B. Kuppenheimer Fund.

sion of the incidence and significance of the form without axis deviation. Our attention was directed to the subject because, in the daily observation of routine electrocardiograms, we had noticed several instances in which patients with etiologic causes for an added burden on the left ventricle failed to show the expected electrical deviation. This occurred in some cases even when the classical *S-T-T* deviations in Lead 1, and occasionally in Leads 1 and 2, expected in left ventricular preponderance were present. Some years ago, Cohn⁶ drew attention to the fact that an abnormal *T* wave in Lead 1 was more stable than axis deviation under the influence of change in heart position. He, therefore, predicted that future experience might reveal that these *T*₁ changes would be of greater diagnostic importance than axis deviation. A few years later, Barnes and Whitten² pointed out that 20% of patients who present *T* wave negativity in Lead 1 as a sign of left ventricular strain do not show any electrical deviation, from which they concluded that the factors causing axis deviation probably differ from those which determine the *T* wave negativity. In the present report we wish to present the results of a systematic analysis of electrocardiograms taken routinely on patients with lesions which primarily increase the work of the left ventricle. This study was undertaken in order to determine the frequency of appearance of the type of electrocardiogram without axis deviation in such conditions, and to evaluate its possible causes.

The cases used were selected at random from the hospital or clinic files. The greatest percentage of records used were from patients with a sustained arterial hypertension showing at several different sittings a diastolic pressure of 90 mm. Hg or more. The patients with acute infections, such as acute hemorrhagic nephritis, pneumonia and those with thyrotoxicosis were excluded. In addition to the hypertensive group, a number of fully developed syphilitic and rheumatic aortic valvular deformities were included. The history and physical findings of all the cases were carefully reviewed to exclude any cases that might have had a recent or old myocardial infarction, since such a circumstance would complicate the electrocardiographic contour. Furthermore, cases were discarded in which serial tracings cast a suspicion of the presence of a recent myocardial infarction. Finally, all cases with a *QRS* duration of 0.12 second or longer were also excluded, as were those having a history of receiving large amounts of digitalis or an appearance in the electrocardiogram suggesting excessive digitalization.

Of the 178 cases finally selected, 148 were patients with hypertension, with or without arteriosclerosis, 18 had rheumatic and 12 syphilitic aortic valvular involvement. Serial records were obtained on 72 (40%) of these patients. In 24 of the cases, necropsy had been performed. A teleoroentgenogram was available in each of the 178 cases from which to determine the probable heart size. We

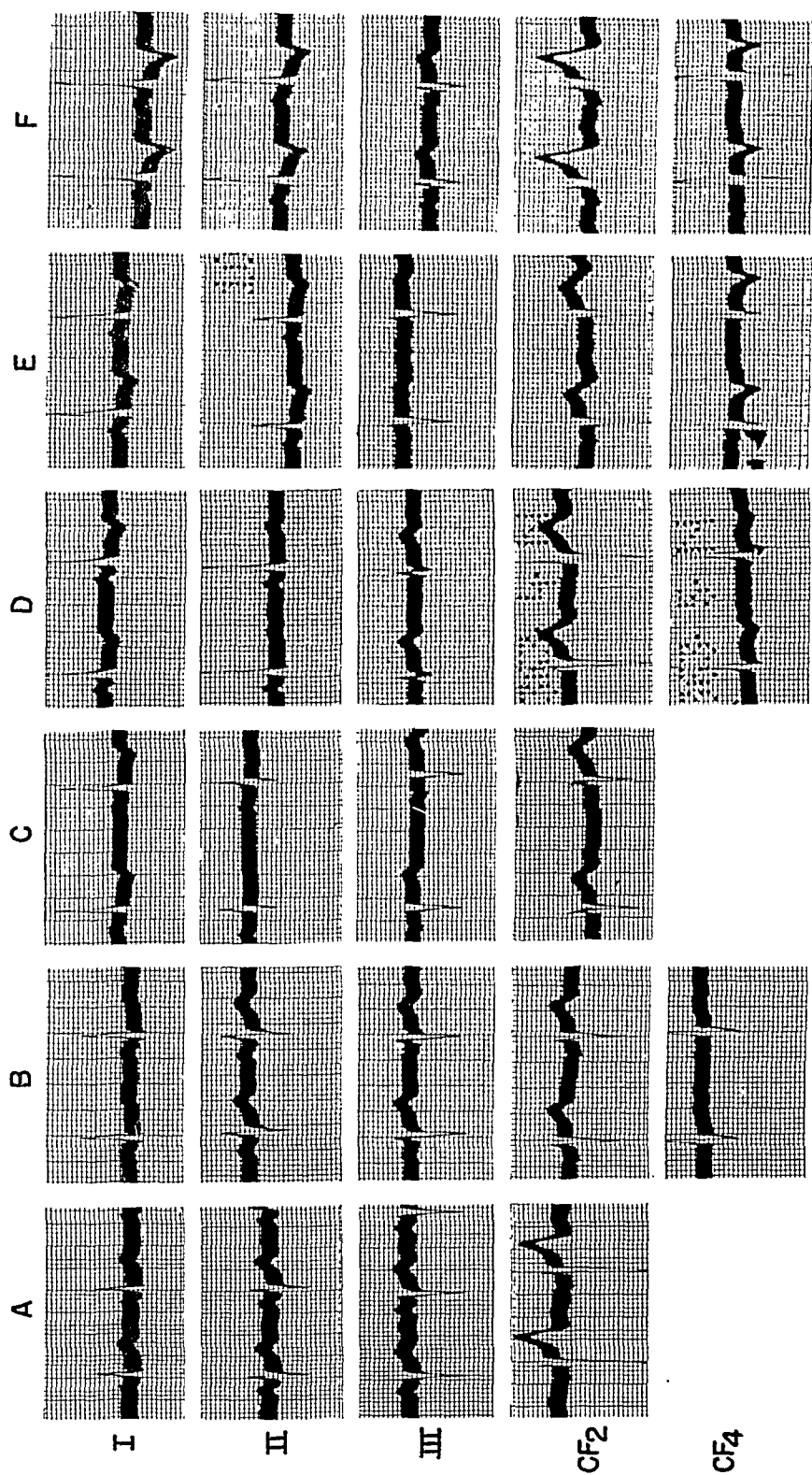


FIG 1.

were able to divide the records in this series into three groups, the first two groups being characterized by axis deviation, one with and the other without the characteristic *S-T-T* changes, and the last, the concordant group, in which the characteristic *S-T-T* alterations were present, but without any axis deviation.

In the first type with axis deviation, the *QRS* complex has its major deflection upright in Lead 1, and inverted in Leads 2 and 3. Furthermore, the *QRS* in Leads 2 and 3 usually have two phases and are of the "S" type, *i. e.*, the final inverted phase is one-quarter or more of the initial upright one. These *QRS* changes are not accompanied by any *T* wave or *S-T* segment abnormalities (Fig. 1, *A*).

In the second type with axis deviation, *QRS* has its major deflection upright in Leads 1 and 2 and *QRS* in Lead 3 is mainly or entirely inverted and of the "S" type. The striking change is in the *S-T-T* segment. In Leads 1 and 3, and occasionally in Lead 2 also, the *S-T-T* segment is deviated in a direction opposite to the major deflection of the *QRS* complex of the lead (Fig. 1, *E* and *F*). Thus *S-T* is depressed and *T* is inverted in Lead 1 (and 2) and *S-T* elevated and *T* upright in Lead 3. It is significant that the convexity of *S-T* is directed upward in Lead 1 (and 2) and downward in Lead 3.

Less advanced and intermediate forms of the two types are also to be found (Fig. 1, *D*) in which some of the features are absent, and mixed types combining the abnormalities of the two foregoing groups are common (Fig. 1, *B* and *C*).

In the group without axis deviation, the concordant group, the major *QRS* deflection is upright in all three leads and the classical *S-T-T* changes described in the second type with axis deviation

LEGEND FOR FIG. 1.

FIG. 1.—Examples of Type 1, Type 2, and the mixed type of left ventricular strain.*

Segment *A*. A young woman of 30 with chronic glomerulonephritis and hypertension (180/120) of many years' duration. It is a typical example of Type 1 as described in the text.

Segment *B*. A man of 65 with arterial hypertension of many years' duration associated with dyspnea on exertion and angina pectoris. It shows a mixed type in that *S-T₁* is depressed and *T₁* is tiny and it has an equiphasic *QRS₂*.

Segment *C*. A man of 69 with hypertensive and arteriosclerotic heart disease. It shows a more usual mixed type, in that the typical *S-T-T* complex in Lead 1 is directed opposite to the major upright *QRS* deflection and *QRS₂* is diphasic and has an *S* wave.

Segment *D*. A woman of 64 who had a marked hypertension (190/120) for at least 2 years associated with symptoms of dyspnea, headaches, and dizziness. It shows the second type of left ventricular strain as described in the text. The *S-T-T* complex in Lead 1 is classical but Lead 2 shows an earlier stage.

Segment *E*. A woman of 50 who had arterial hypertension, averaging 184/110 for many years associated with symptoms of dyspnea on exertion and headaches. It shows another example of Type 2 in which Lead 2 resembles Lead 1.

Segment *F*. A male of 60 who had arteriosclerotic and hypertensive heart disease, with a blood pressure of 190/110 and dyspnea and angina pectoris on exertion, for many years. It shows another example of Type 2 but more advanced than Segment *E*.

* In all instances of this and subsequent records *QRS* is normal in duration, unless otherwise specified.

is found in Lead 1 and occasionally in Lead 2 (Fig. 2). In this series no instance was found in which the major phase of *QRS* was inverted in all the limb leads.

Results. Frequency of Types. The greatest number of records seen fell into the second type with axis deviation; 52 cases (29%) were classically of this variety. In 10 of these, the records differed from the classical pattern, in that T_3 was also inverted. The next

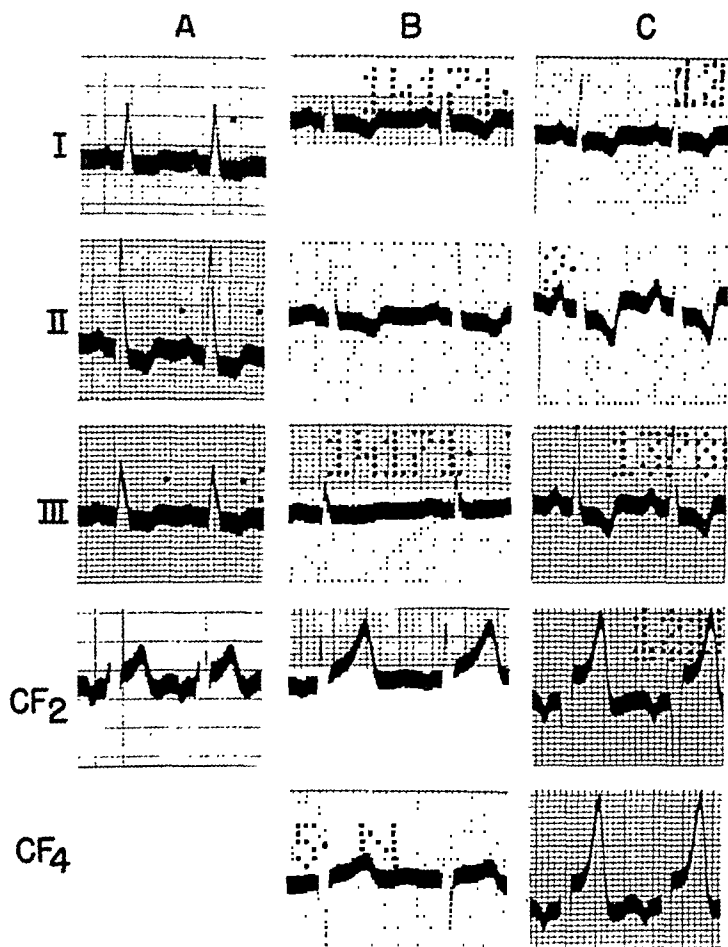


FIG. 2.—Examples of concordant type of electrocardiograms seen in left ventricular strain.

Segment A. A male of 51 whose autopsy findings are discussed in the text. It shows an upright *QRS* in all three limb leads and the *S-T-T* complex oppositely directed.

Segment B. A male of 65 whose autopsy findings are also discussed in the text. It shows the same type of record as A with a more classical *S-T-T* configuration in Leads 1 and 2.

Segment C. A male of 28 with a marked rheumatic aortic stenosis and mitral stenosis and insufficiency without any evidence of congestive heart failure. The findings in the limb leads are classical for this type. Note the entirely inverted *QRS*, the abnormally elevated *S-T* segments, and the abnormally tall *T* waves in the chest leads. These chest lead abnormalities, suggestive of coronary insufficiency, can all be attributed to the left ventricular strain.

most frequent pattern resembled the second type with axis deviation, except that the *T* wave in Lead 1 was small and upright, instead of being inverted (Fig. 3, *B*); at the same time the *S-T* segment was depressed 0.5 to 2 mm. below the isoelectric line in Lead 1, or Leads 1 and 2, and had a downwardly directed convexity. This form, as noted later, is an earlier stage in the evolution of the electrocardiogram to the more classical pattern. There were 38 cases (21%) of this variety.

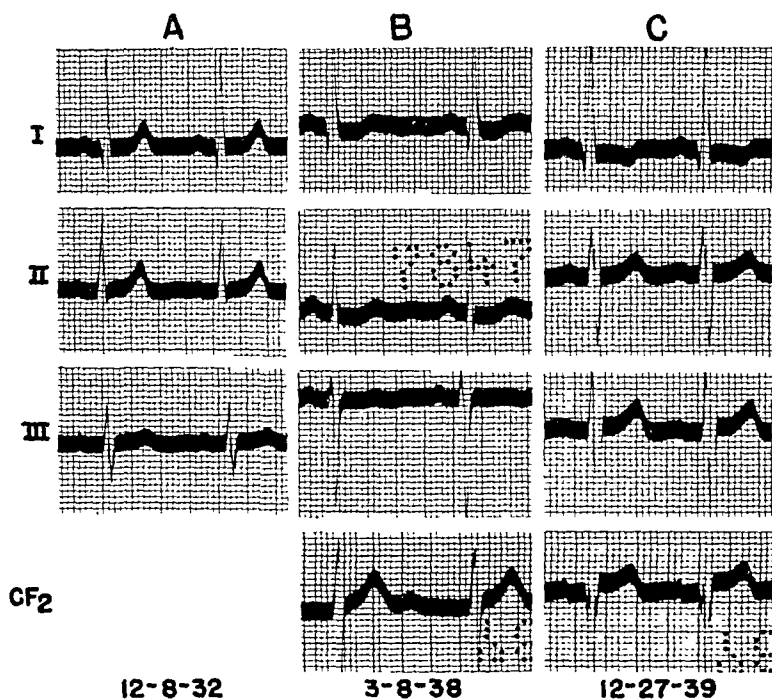


FIG. 3.—Shown to illustrate the progression of the electrocardiographic changes from the second to the mixed type.

This woman of 46 first discovered that she had arterial hypertension in 1932, at which time record *A* was taken. It shows a normal *QRST* complex in all three leads with only a left axis shift (normal) indicated by an *S* wave in Lead 3.

When Segment *B* was taken in 1938, her blood pressure was 255/150 and she now complained of dyspnea on exertion, headaches and nocturia. It shows depressed *S-T* segments in Leads 1 and 2 and smaller *T* waves in these leads. *QRS*₂ has become mainly inverted but *CF*₂ has a normal appearance. This is an early stage of the second type.

One and a half years later, when Segment *C* was taken, the *S-T* in Lead 1 has developed an upward bowing and the *T* wave is now inverted. *QRS*₂ has now become diphasic, with an *S* wave, and *T* in Leads 2 and 3 are taller. In *CF*₂, the *QRS* has become entirely inverted and notched, the *S-T* slightly more elevated and the *T* wave smaller. This record is a typical mixed type.

The first type with axis deviation was found in 22 instances (12%). There were 22 records (12%) of the mixed variety with axis deviation; in these the *QRS* pattern was of the first type but the *S-T-T* in Lead 1 (and Lead 2) was of the second type with axis deviation.

There were 17 cases (10%) in which there was no axis deviation

but the typical $S-T-T$ changes were found in Lead 1. In 11 others (6%), the only abnormalities noted in the record were $S-T$ depression in Lead 1, or Leads 1 and 2. A simple left axis shift, in which only QRS_3 was mainly or entirely inverted, but with no abnormalities of the $S-T-T$ complexes in Leads 1 and 2 was seen in 12 (7%) patients (Fig. 3, *A*). In 2 of these T_3 was also inverted. There were 4 records (3%) which could not be classified in the above groups because of the presence of marked low voltage of the ventricular complex in all 3 leads.

The most characteristic feature present throughout the series was the classical $S-T-T$ deviation in Lead 1. This was found in 91 patients (51% of the entire group). There was no axis deviation in 19% of these, which conforms rather closely to the frequency in Barnes and Whitten's series.²

Chest Lead Appearance. The configuration of the chest leads in all of the above groups was similar. In CF_2 , the lead used most commonly by us, there was a consistent diminution in the height of the initial upward phase of the QRS complex (Figs. 1, *A*, *B*, *C* and *F*, and 2, *A*). An initial upward deflection of 3 mm. or less was noted in 77% of the cases. There were 9 records in which QRS was entirely inverted (Figs. 1, *E*, and 2, *C*). Occasionally QRS was W in type or M in type. The $S-T$ segment was usually normal and only rarely was it elevated more than 3 mm. (Fig. 2, *C*). The T wave was normal in height, except on rare occasions when it was tall (Fig. 2, *C*). T wave inversion was noted in 7 instances and in some of these QRS was chiefly or entirely upright.

For the past 2 years we have also used the chest lead CF_4 in the routine examination of our patients, but we cannot present definite percentage data as to the commoner types found because our series is too small. In general, it has been our experience that when the heart is definitely enlarged so that the electrode is not at the apex, CF_4 resembles the usual type noted in CF_2 (Figs. 2, *B* and *C*, and 5, *B*). Our observations indicate that when the heart is not greatly enlarged and the chest electrode is near the apex, the QRS complex tends to be upright and the $S-T-T$ downwardly directed, an appearance similar to Lead 1 (Figs. 1, *D*, *E* and *F*, and 7).

Necropsy Series. Predominant left ventricular hypertrophy was found in all 24 patients on whom autopsy reports were available. Cases are illustrated in Figures 2, *A*, 2, *B*, and 6. There was no definite correlation noted between the heart weight and the electrocardiographic appearance. In the 7 cases that had an inversion of T_1 , the smallest heart weighed 350 gm., the largest 540 (average heart weight, 450 gm.). A similar distribution was noted in those patients with the first type of electrocardiogram with axis deviation and the average heart weight was approximately the same. The largest heart in this whole series weighed 850 gm. and showed a normal left axis shift (QRS_3 inverted) and a diminution in the

height of the *T* waves in the limb leads. All of the hearts showed varying degrees of coronary sclerosis and myocardial fibrosis, but there were none with evidence of old or recent myocardial infarction. The average age of the patients in the autopsy series was 60 years.

Correlation with Roentgen Ray Heart Size. There was a similar lack of correlation of electrocardiographic appearance and heart size as judged by the Roentgen ray silhouette. Our series discloses that the various types of electrocardiographic patterns enumerated above can be found with relatively small hearts as well as with grossly enlarged ones. In the appraisal of cardiac size by the teleoroentgenogram, we used cardiac configuration and the simplest cardiac measurements, *i. e.*, the ratio

greatest transverse diameter of the heart

greatest transverse diameter of the thorax at the level of the left diaphragm

We realize that with such a simple cardiothoracic measurement, minor degrees of cardiac hypertrophy will not be evident, but with an evaluation of contour and physical findings, a reasonable degree of accuracy is possible. Hodges⁷ has stated that due to the diverse physical stature of individuals, no procedure of recording heart size is infallible and that fluoroscopic examination is the best control. We have arbitrarily accepted a cardiothoracic ratio of 50% or more (in the adult) as evidence of a larger than normal heart. Seventy-seven per cent of the entire series had a cardiothoracic ratio of 50% or more, although it was noted that 92% of the patients with *T*₁ negativity showed enlarged hearts. The group that showed the greatest percentage of grossly enlarged hearts (60% of the chest diameter or more) was the concordant group. It was seen in 62.5% of these cases.

Changes in Serial Electrocardiograms. In reviewing the cases that had many records over a period of years, it was noted that there was a characteristic progression in the development of the classical types. The earliest change usually noted was an axis deviation with the record still within normal limits (Fig. 3). Later a depression of the *S-T* segment in Leads 1 and 2 developed. Associated with this, there was a decrease in the amplitude of the *T* wave in these leads (Fig. 3). At this stage, the depressed *S-T* segment is concave upward. In the later progression, which may not appear for several years, the *S-T* assumes a convex upward curve in Lead 1 (and 2) and the *T* wave in these leads becomes at first diphasic, and later inverted with asymmetrical limbs. This progression caused several cases starting as a Type 1 with axis deviation to change to a mixed type. This progression in cases of the second type with axis deviation shows the steps by which the classical form is attained. In addition to the *S-T-T* evolution, *QRS* alterations are sometimes seen in Type 2 so that *QRS*₂ tends to become of the "S" type, resulting in this way in the appearance of the

mixed type. In several instances it was observed that a record normal at the start may develop into the concordant type without axis deviation (Fig. 4), or into Type 1, Type 2 or the mixed type with axis deviation. Occasionally, a Type 2 with axis deviation was seen to lose its axis deviation and conform to the concordant type without axis deviation (Fig. 6). Viewing our entire experience, we are impressed that the progressive changes of the S - T - T' deviations in Lead 1 to the classical pattern is the most characteristic feature in the electrocardiograms of patients with protracted

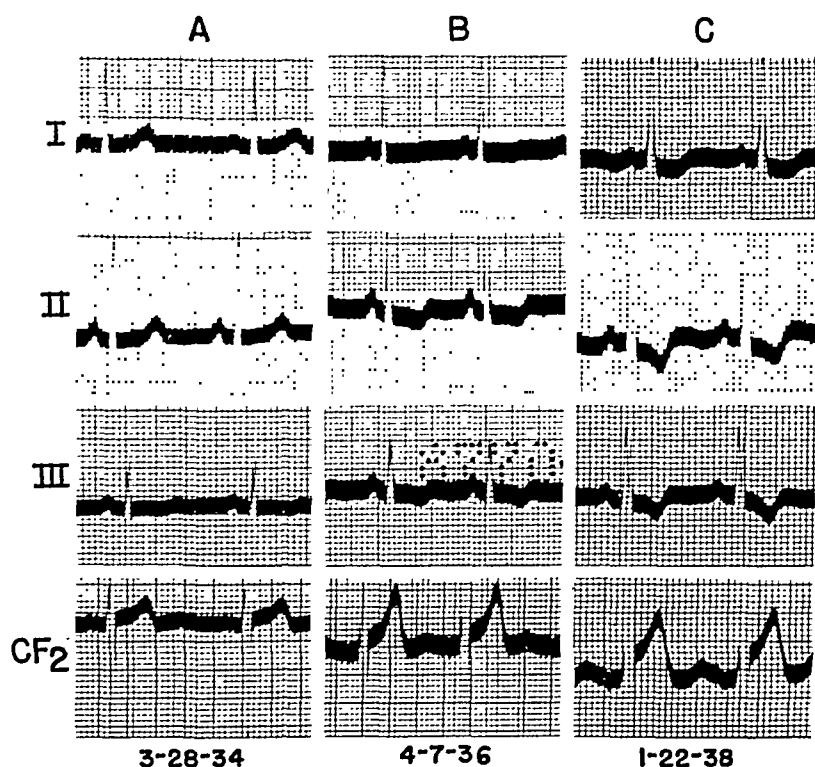


FIG. 4.—An example of the development of the concordant type of left ventricular strain.

This patient, a female of 41, had had a marked arterial hypertension since 1934 and since then had had several episodes of congestive heart failure from which she recovered. Segment A is a record probably within normal limits. Segment B, taken 2 years later, shows S - T depressions and T -wave inversions in all three leads. In addition, the initial upward phase of QRS , has diminished in amplitude, the S - T segment has become slightly more elevated and the T wave taller. Segment C is similar to Segment B except that the T waves have become deeper and S - T more elevated. The progressive nature of the changes, their late development and their persistence, as shown here, are characteristic of left ventricular strain.

left ventricular strain (Figs. 3 and 4). The long period involved in its evolution, and its persistence, once it has developed, distinguishes the left ventricular strain electrocardiogram from that seen in myocardial infarction, even aside from the difference in their detailed contour when fully developed (Figs. 5 and 6).

Concordant Type of Left Ventricular Strain. In the 17 patients who presented the classical *S-T-T* deviation of left ventricular strain in Lead I, without showing any electrical axis deviation, 11 cases had hypertensive cardiovascular disease and 9 of these had had at least one episode of congestive heart failure. In 4 others, chronic rheumatic aortic valvular disease with an associated mitral stenosis and insufficiency was present and in 2 patients syphilitic aortic

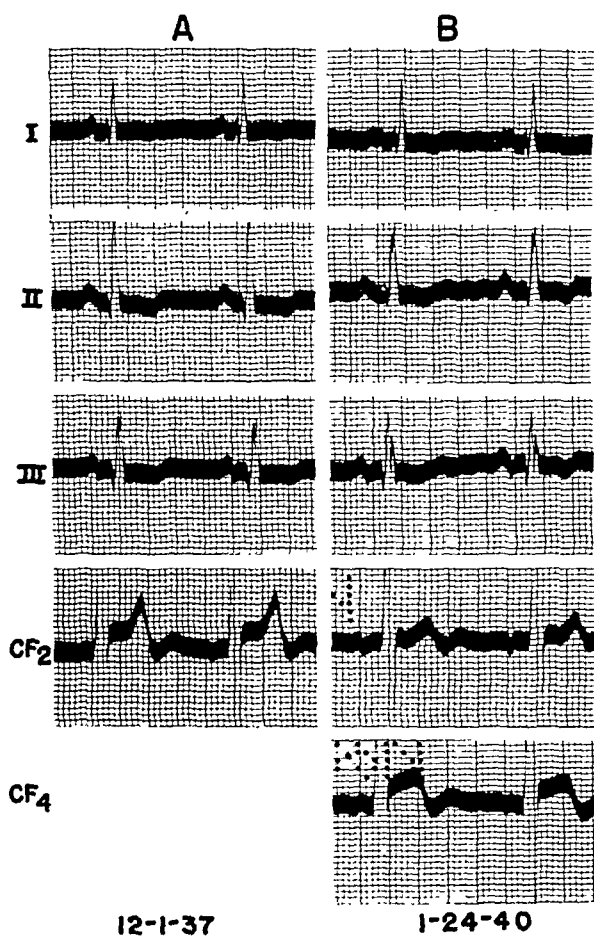


FIG. 5.—Illustrates the persistence of the electrocardiographic changes, once they have appeared, in an instance of the concordant type of left ventricular strain.

The patient, a male, of 52, had a free syphilitic aortic regurgitation and had been in congestive cardiac failure on many occasions. Segment A, taken in 1937, shows the absence of axis deviation and the *S-T-T* complexes directed oppositely to the *QRS* in all three leads. *CF*₂ is normal in appearance. A record, Segment B, taken 3 years later, shows a pattern almost identical with Segment A, except that *T*₄ is smaller. *CF*₄ is normal in configuration.

insufficiency (Fig. 5) was the cause. In both of the latter, congestive heart failure was also present.

Three of the above patients, with the concordant type of left ventricular strain, were examined at necropsy. One of these, who

had hypertension for many years and had been in congestive failure several times, revealed a markedly enlarged heart, weighing 625 gm., involving chiefly the left ventricle but also the right ventricle to a moderate degree. In addition, there was a moderate degree of coronary sclerosis and myocardial fibrosis, without myocardial infarction (Fig. 6). The second patient, who had been afflicted with allergic bronchial asthma since childhood and had developed arterial hypertension in his later years, was seen in the hospital in terminal congestive failure. Necropsy showed a tremendously enlarged heart, weighing 830 gm., with both left and right ventricles involved.

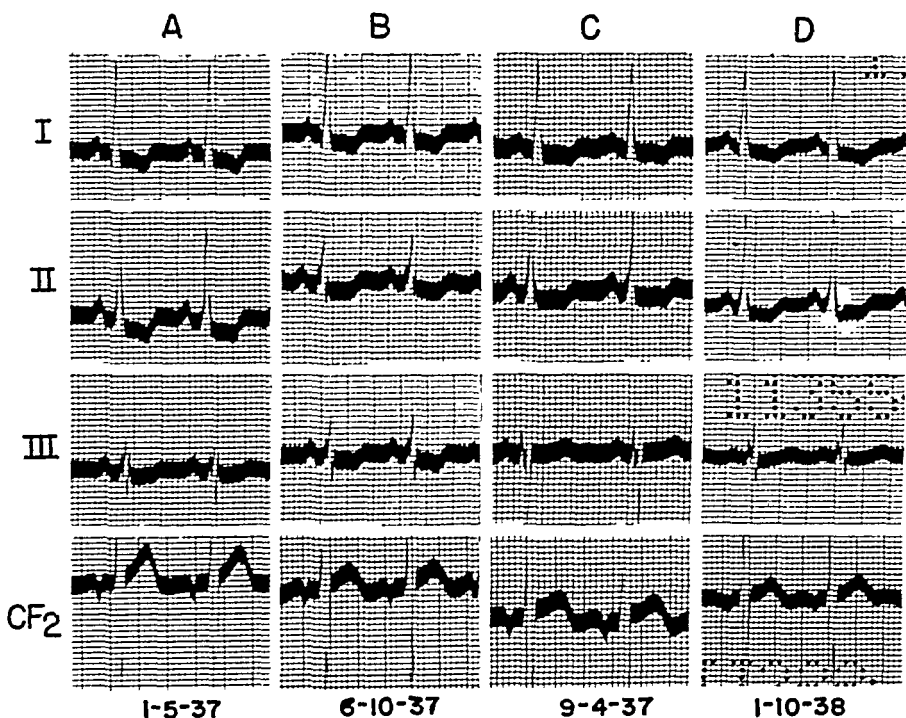


FIG. 6.—These records, taken over a period of 1½ years on a male of 61, with hypertensive cardiovascular renal disease (whose autopsy findings are discussed in the text) shows the characteristic *S-T-T* deviations in Leads 1 and 2 found in left ventricular strain. The change in axis from an inverted *QRS*₃ (as in Segments A and C) to a mainly upright *QRS*₃ (as in Segments B and D) without any material change in Leads 1 and 2 during these periods, is again illustrative of the comparative diagnostic value of the *S-T-T* changes as contrasted with axis deviation. It will also be noted that *CF*₂ has undergone very little alteration during this time, retaining its normal appearance except for the inverted *P*₄. In this instance no evidence of a recent or old myocardial infarction was found proving that left ventricular strain can cause this contour.

There was no coronary occlusion nor myocardial infarct, but a moderate amount of coronary sclerosis and myocardial fibrosis was present. Arteriolar nephrosclerosis, bilateral hydrothoraces and emphysema were also present (Fig. 2, A). The third patient, who also had hypertension for many years, died in the hospital of an

unrelated cause. At necropsy, the heart weighed 450 gm. and there was left ventricular hypertrophy and a normal right ventricle. A massive left hydrothorax, with displacement of the heart to the right, noted previously in the Roentgen ray examination, was found to be due to a pleural fibrosarcoma. A moderate amount of coronary sclerosis was present (Fig. 2, *B*).

Inversion of the *T* wave in all three limb leads was found in 8 of the 17 patients of the concordant group (Figs. 2, *A*, 2, *C*, 4, *C*, 5 and 6, *B*). Four of these patients were in the hypertensive group, 2 in the rheumatic and 2 in the syphilitic aortic valvular group. In 2 instances of the concordant series, in which serial records were taken over a period of years, progressive changes were noted, culminating in the classical *S-T-T* deviation in Lead 1, but no axis deviation was noted at any time (Fig. 4). Both of these patients had arterial hypertension, one with a history of frank congestive failure, the other only with symptoms of dyspnea on exertion.

Discussion. It is thus to be noted that the most constant feature of the electrocardiograms in primary left ventricular strain is the classical *S-T* deviation occurring in Lead 1. A progressive evolution of the *S-T-T* segment to this stage was seen occurring in cases which at first had a normal left axis shift, in those which started with the first type of left ventricular strain with axis deviation, and even in those which were first observed without any axis deviation. Although axis deviation is found in the majority of the cases, and is a major sign of preponderant hypertrophy, we have found that in about one-fifth of the cases no electrical axis deviation may be seen.

Our analysis suggests that the absence of electrical axis deviation is due to the neutralizing effect of either a concomitant right ventricular hypertrophy or of a change in the position of the heart. The effect of position change is shown clearly in Figure 7, in which a respiratory change in the position of the heart causes *QRS*₃ to become upright in two beats, and at the same time *T*₃ to become inverted and *S-T*₃ depressed. This change shows how easily the concordant type could be caused by a lasting change in the heart's position. The fact that the commonest causes of right ventricular hypertrophy is a preceding left ventricular hypertrophy,²¹ a fact now well established, would suggest that this mechanism would be an important one for the occurrence of an electrocardiogram with left ventricular strain without axis deviation. In our series, this was the probable factor in the majority of our cases. Hypertension, syphilitic aortic insufficiency and rheumatic aortic valve involvement all can lead to this. The frequent presence of an associated mitral valve deformity makes the combination of right and left ventricular hypertrophy more common in rheumatic aortic valvular disease. The superposition of right ventricular strain in patients with left ventricular strain may come about because of associated lesions such as chronic pulmonary disease²⁰ or chest deformity which

increase the pulmonary arterial pressure. The existence of such concomitant factors which tend to nullify the electrical deviation in left ventricular preponderance must be fully recognized. In these cases in which the primary strain on the left heart ultimately causes strain on the right heart, the condition of absent axis deviation may be a sign of advanced stage of strain.

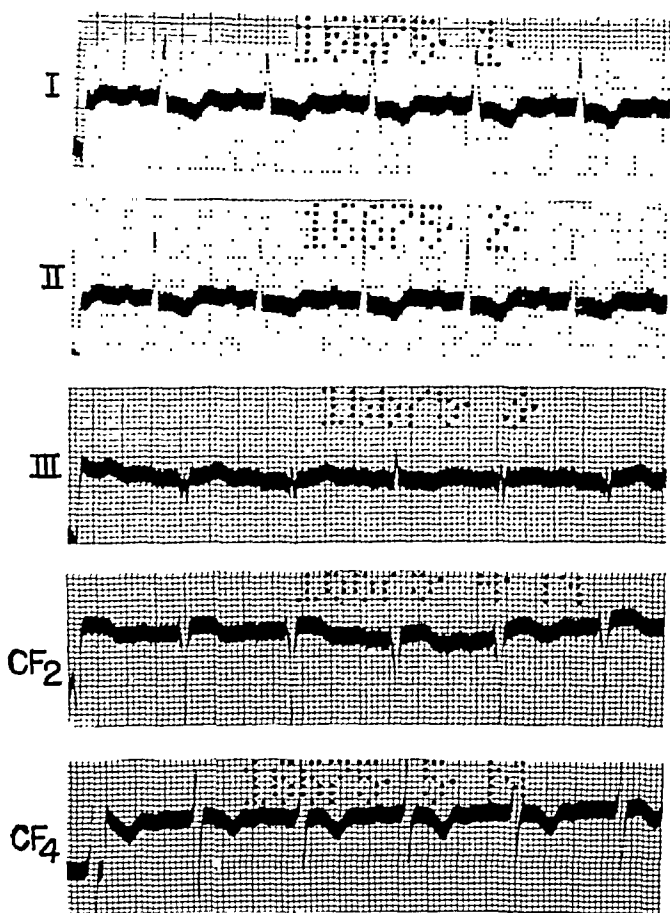


FIG. 7.—Shows the effect of respiratory changes in position of the heart in neutralizing axis deviation from a woman of 52, with arterial hypertension (160/120). It will be seen, in Lead 3, that the *QRS* changes gradually from an entirely inverted complex to an upright one with opposite deviation of the *S-T-T* complex. The *S-T-T* in Leads 1 and 2 undergoes only slight changes during comparable periods, as does *QRS*. Such respiratory changes, although of greater degree than usually present, again show the comparative value of the *S-T-T* changes in Lead 1. It also shows how readily the second type of left ventricular strain can shift to the concordant type.

Apparently, those factors nullifying axis deviation, do not affect the *S-T-T* changes as readily. Thus the *S-T-T* changes may remain as the sole diagnostic clue of the presence of a long-standing and severe left ventricular strain. This experience of ours therefore

lends further evidence to Cohn's belief⁶ that the *T* wave changes are as important as axis deviation and to Barnes'¹ assertion that absence of axis deviation does not minimize the significance of *T* wave inversion in Lead 1.

The full-blown changes present in Lead 1 in left ventricular strain must not be confused with those instances of *T*₁ inversion due to numerous other causes. Katz^{3a} has presented a critical survey of the various causes of *T* wave negativity. The most commonly mistaken diagnosis is that of a recent myocardial infarction of the anterior wall. The use of serial records in cases of confusion will show the characteristic evolution of the major electrocardiographic changes in infarction.^{3b} It is a pertinent feature of records denoting left ventricular strain that the changes are slow in their evolution and more or less permanent once they have appeared.^{13,19} It is, however, true that on occasion a *T*₁ inversion due to chronic coronary insufficiency may persist unchanged.^{3a} This factor of persistence of abnormalities may also be used to differentiate those cases of *T*₁ negativity occurring in acute nephritis^{11,15} and in acute infectious diseases.¹⁴ A perusal of the clinical history and findings will help to clarify the diagnosis in cases of doubt. One important drug that occasionally may mimic the *S-T-T* changes is digitalis.^{4,8b} Digitalis most commonly produces a depression of the *S-T* interval but this depression consists of a flattening of the *S-T* which makes this segment merge imperceptibly with the *T* wave, instead of the depressed *S-T* having an upward convexity separating it clearly from the inverted *T* wave as seen in left ventricular strain. In the intermediate stages of digitalis deformity, confusion may arise but the withdrawal of the drug will permit an evaluation, although several weeks may be required before the digitalis effect wears off. The chest leads are seldom of much assistance.

It can be readily appreciated that left ventricular strain is not the only etiologic agent for *T*₁ negativity or for the special *S-T-T* combination, nor is it our intention to imply this, but it is a major factor in persistent cases and should be so recognized after dismissing other possibilities.

The classical *S-T-T* deviation in Lead 1 is evidence of widespread changes in the retreat of activation of the heart. In part this is attributable to the increase in muscle mass with a consequent tendency for the pattern of invasion to determine the pattern of retreat. In addition, however, widespread changes in the conduction system which develop in hypertrophied hearts may be an important contributing factor. This damage to the conduction system may be insufficient to prolong *QRS* while giving the electrocardiogram the other characteristics of intraventricular block. That this latter factor may play a rôle is shown by the gradual evolution of the left ventricular strain curves in a number of cases into the common type of intraventricular block. The damage to the con-

duction system may result from chronic coronary insufficiency, consequent upon coronary sclerosis and arterial narrowing to which the conduction system is more susceptible than ordinary heart muscle.²³ Coronary sclerosis is not the only factor involved in these conduction disturbances as these changes occur in relatively young patients who have chronic rheumatic valvular disease (Fig. 2, C). Wearn *et al.*¹⁸ have shown that as the heart hypertrophies the capillary supply becomes insufficient and not commensurate with the increase in mass of the myocardium. This is probably an important factor in the production of conduction disturbances in hypertrophied hearts and could explain the 4 cases of Rykert and Hepburn¹⁹ in which at autopsy myocardial hypertrophy was found without other abnormalities and with normal coronary arteries.

These $S-T-T$ changes resulting from abnormalities in conduction must not be confused with those changes resulting from injury currents even though both are the result of coronary insufficiency. The $S-T$ segment deviation expressing injury currents is not always deviated in a direction opposite to the major QRS deflection as is the case with a conduction disturbance. It has its convexity directed in the same direction as its deviation, unlike the case with a conduction disturbance where the convexity is in the opposite direction to the deviation of $S-T$. Furthermore, in injury currents the T wave is in the opposite direction to the $S-T$ deviation, while in the full-blown conduction disturbance the T and $S-T$ are deviated in the same direction. The close relation of the left ventricular strain curve to intraventricular block is shown by the development of the latter in long-standing cases. In such circumstances the appearance of the curve does not change usually except that QRS becomes prolonged beyond 0.12 second. It is true that occasionally injury currents may produce $S-T$ segment or T wave changes in cases of left ventricular strain which are confusing, and sometimes the early stages of left ventricular strain give records which may be mistaken for those of injury currents. Usually, however, the QRS changes that occur and the typical $S-T-T$ patterns of injury currents are sufficiently distinct from those resulting from the conduction disturbances seen in left ventricular strain (and in the common type of intraventricular block). In some instances, little help is to be expected from the chest leads in this differentiation, since the $QRST$ findings may be similar regardless of whether the cause is injury currents or a conduction disturbance.

The importance of recognizing the $S-T-T$ changes in Lead 1 of left ventricular strain lies in the evaluation it affords in determining the normality of axis deviation. We are designating any record that has merely an inversion of the major phase of QRS_3 , with no associated $S-T-T$ changes in Lead 1, or Leads 1 and 2, as a normal phenomenon provided the inverted phase is not of the Q type, and are labelling this, left axis shift. It has been adequately shown⁵

that about one-fourth of normal patients of middle age will show this simple left axis shift, and that this is especially true when obesity¹⁶ or pregnancy¹⁰ is present. The presence of an associated inversion of QRS_2 , in addition to that of QRS_3 without the Q pattern, is to be regarded as probable evidence of left ventricular strain, and is called the first type with axis deviation. It has nevertheless been shown that such marked axis deviation may be found in

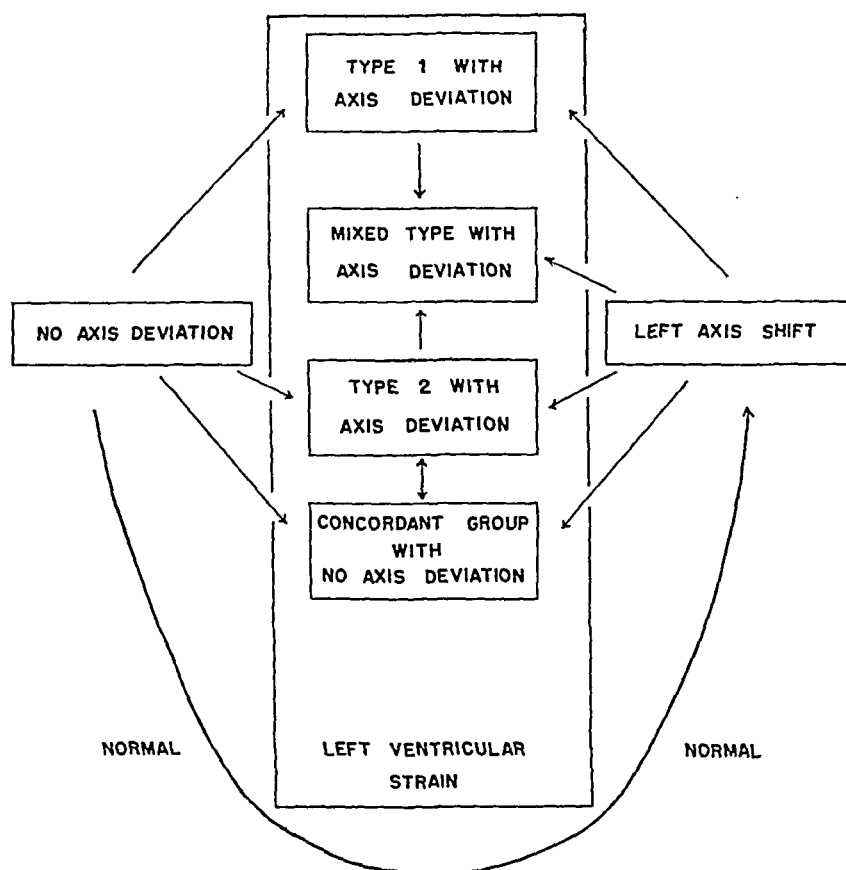


FIG. 8.—The interrelationship and the manner of their progression of the various types of electrocardiograms seen in left ventricular strain, found in the present series.

brown atrophy of the heart,⁹ and therefore may not always be indicative of left ventricular hypertrophy. While the normal left axis shift or the first type with axis deviation may be found in cases of left ventricular hypertrophy, the presence of the $S-T-T$ deviations described in this report are the distinguishing features of prolonged left ventricular strain, and are indicative to us of the presence of left ventricular preponderance. With these $S-T-T$ changes, the presence of axis deviation is not a necessary accompaniment for the diagnosis of differential predominant ventricular strain and is in fact sometimes absent.

The practical importance of recognizing these changes in Lead 1 occurring in left ventricular strain is obvious. Especially one must be careful not to label the case an instance of recent myocardial infarction with its clinical implications. The classical forms may be present in patients who are ambulatory and have a circulatory system consistent with a moderately active existence. The concordant group is as important and as diagnostic as the classical type of left ventricular preponderance electrocardiograms and as such must be recognized.

The relationship in the development of the various types of electrocardiographic pattern in left ventricular strain according to our experience is summarized diagrammatically in Figure 8.

Summary. 1. The electrocardiographic patterns seen in 178 instances (24 necropsied) of left ventricular strain are described.

2. The characteristic development of the classical *S-T-T* complex in left ventricular strain is emphasized.

3. The classical types and intermediate forms are described and the natural evolution of these are presented.

4. Approximately 15% of the total cases in the present series did not show any axis deviation and 62.5% of these had the classical *S-T-T* deviation in Lead 1. This latter type is called the concordant type of left ventricular strain. It formed 19% of all the cases with characteristic *S-T-T* changes in Lead 1.

5. It was not possible to correlate heart size and the type of electrocardiographic pattern in left ventricular strain.

6. Accompanying right ventricular strain, either as a late result of left ventricular strain or of an associated independent cause, and changes in the heart's position are the probable chief causes for lack of axis deviation in the concordant type of left ventricular strain.

7. The *S-T-T* deviation in left ventricular strain is attributable to a disturbance in the retreat of activity in the ventricles, in part due to the hypertrophy itself and in part secondary to coronary insufficiency.

8. The practical importance of recognizing the concordant type of electrocardiogram in left ventricular strain is emphasized.

We are indebted to the several physicians of the hospital staff for permission to use their cases, to Dr. R. Arens of the X-ray Department for use of the teleroentgenograms and to Dr. O. Saphir of the Pathology Department for use of the necropsy reports. We wish to acknowledge the assistance of Drs. J. Post and H. Sugarman in the compilation of the material.

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THE ALTERATIONS OF THE T-WAVES CAUSED BY A CHANGE OF POSTURE.

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IN one of his early classical papers on the normal electrocardiogram Einthoven⁴ described the alterations which occur with change of position of the patient. Since then the subject has been investigated frequently, but for many years attention was directed exclusively to the alterations of the initial ventricular complex. There is a rather voluminous literature dealing with changes of this type noted after change of position and movement of the diaphragm.³

It has also been known for a long time that the *T*-wave may become altered and even inverted on change of posture; in fact, in 1910, Grau⁷ described alterations of the *T*-waves in healthy subjects as the result of gastric distention. He also found changes in the *T*-waves with change of posture. More recently Leimdoerfer described alterations of the *T*-waves in Leads I and II upon change from the recumbent to standing posture. He found inversion of the *T*-waves and depression of the *S-T* segments, especially in Leads I and II, after prolonged standing in patients with myocardial damage, but never in healthy individuals. He recommended that the electrocardiogram be taken after standing for 10 to 15 minutes as a functional cardiac test. At the same time, however, Åkesson found alterations of the *T*-waves when the normal subject maintained the erect posture, and explained them as the result of an orthostatic anemia of the heart; this is caused by a redistribution of blood in the standing individual. In the past few years several studies have been undertaken with regard to these changes. Some investigators have interpreted the alterations of the *T*-waves as a

normal phenomenon,^{5,20} while others have regarded them as a sign of myocardial damage,^{1c,18,19} or evidence of a pathologic heart.^{9,13}

The appearance of these changes in the normal may be regarded as a demonstrated fact. However, there is no unanimity of opinion with regard to the mechanism involved. A reinvestigation of this question was undertaken and an endeavor was made to find a satisfactory explanation for it. In this study the alterations of the final deflection have received primary consideration and discussion.

Results. All our investigations were conducted on normal adults without any evidence of heart disease; the age of the patients ranged between 20 and 30. Thirty-five patients had electrocardiograms taken in the supine position and then were requested to stand for a period not exceeding 12 minutes. Electrocardiograms were taken at short intervals when the patients were in the upright position. The results were fairly uniform whether the electrocardiograms were taken immediately or after 12 minutes of standing. Table 1 shows the results with regard to alterations of the form of the *T*-waves, as compared with the *T*-waves obtained when patients were recumbent.

TABLE 1.—ALTERATIONS OF *T*-WAVES.

	Lead	No. of cases	No. showing diminution	No. showing increase.	No. showing no change.
Alterations of <i>T</i> -waves on change of position from horizontal to vertical	I	34	22	4	8
	II	35	31	0	4
	III	34	31	0	3
Alterations of <i>T</i> -waves on deep inspiration	I	15	15	0	0
	II	15	14	1	0
	III	15	8	4	3
Alterations of <i>T</i> -waves on deep expiration with abdominal pressure	I	15	0	15	0
	II	15	0	13	2
	III	15	12	2	1

The changes were characterized by a depression of the height of the *T*-waves in all leads. The change in Lead I, however, was very slight, whereas in Lead II, and especially in Lead III, it consisted of a marked flattening or inversion of the *T*-wave. In only 3 cases did the *T*-wave remain unchanged in Lead III when the patient stood. In 9 cases a *T*-wave in Lead III, previously positive, became inverted. Depression of the *S-T* segment in Lead III occurred 8 times.

In 28 instances the electrocardiogram was again taken immediately after the patient reassumed the supine position. In all cases the *T*-waves *immediately* returned to their former height and configuration.

In 7 of 35 cases a diminution in the height of the *P*-waves in Lead I occurred while the patient was standing, and in 21 cases an increase in the height of the *P*-waves was observed in Lead III. The alterations of the *QRS* complexes were slight. In 9 cases there was a tendency toward right axis deviation on standing, but this returned to normal immediately on lying down.

Figure 1 shows the electrocardiogram of a 25-year-old male in good health in the supine position (Fig. 1a). The *T*-waves are positive in all leads. The second series (Fig. 1b) was taken while the patient was standing. It shows a lower *T*-wave in Lead I, an almost invisible *T*-wave in Lead II, and an inverted *T*-wave in Lead III. Immediately after lying down the electrocardiogram (Fig. 1c) is again like the first one, taken while the patient was in the supine position.

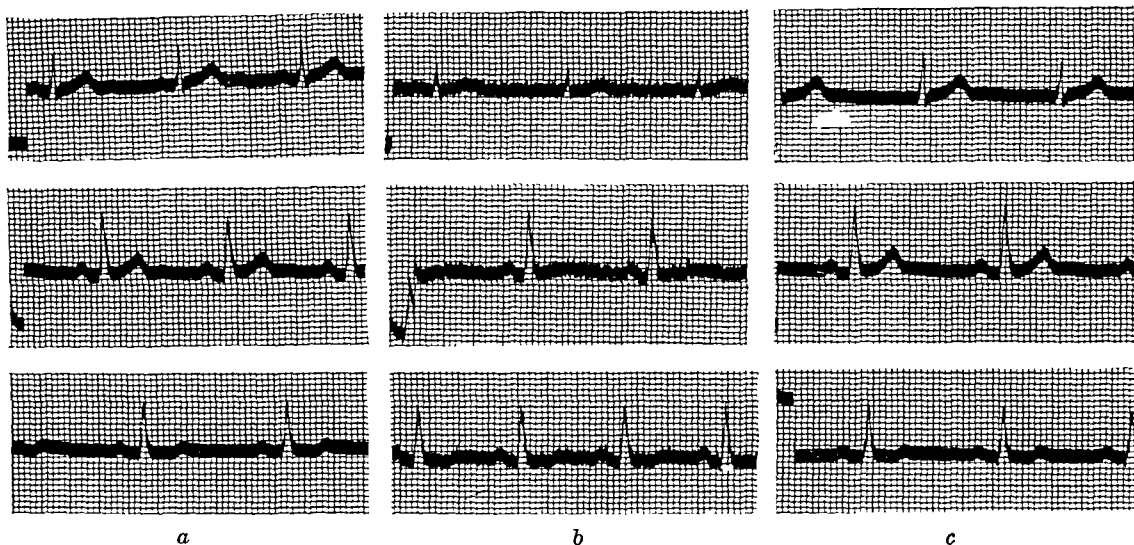


FIG. 1a-c.—a, Patient in the supine position; b, immediately after standing up; c, immediately on lying down.

These results are in full agreement with those of previous workers. Åkesson^{1a} found an inversion of T_3 in 31% of his cases while standing. According to Erkelens the *T*-waves in Lead III became inverted in 15 out of 61 cases while standing, a total of 24.5%.

It has already been proven that the alterations described are not evidence of myocardial damage, since they are just as common in the healthy as in patients with heart disease.^{5,20} In order to rule out the possibility of coronary insufficiency^{18,19} or orthostatic anemia of the heart,^{1b,c} we decided first to examine the electrocardiogram in the standing patient after physical effort in the hope that an eventual disturbance of the cardiac blood supply would be more clearly visible after effort; second, to examine the electrocardiogram after the administration of $\frac{1}{100}$ gr. of nitroglycerine, in the hope of abolishing changes due to a diminished blood supply to the heart.

The exercise consisted in hopping 50 times, first on one foot and then on the other. The electrocardiogram was taken after the exercise in 26 cases with patients in the standing position. In all cases only the usual physiologic changes occurred. The *T*-wave became higher in all leads, the *S-T* segment became slightly de-

pressed, and a formerly inverted *T*-wave (while standing) in Lead III became less inverted, invisible, or even positive. There was never an increased negativity of the *T*-waves or a pathologic depression of the *S-T* segment, immediately or 1 to 5 minutes after the exercise.

The electrocardiogram was also taken after the administration of nitroglycerine ($\frac{1}{100}$ gr.) while the patient was still standing. The electrocardiogram, registered at intervals up to 5 minutes after nitroglycerine was given, showed a tachycardia in 6 out of 30 cases tested, further depression of the *S-T* segment, especially in Leads II and III, and a still further diminution of the height of the *T*-waves.

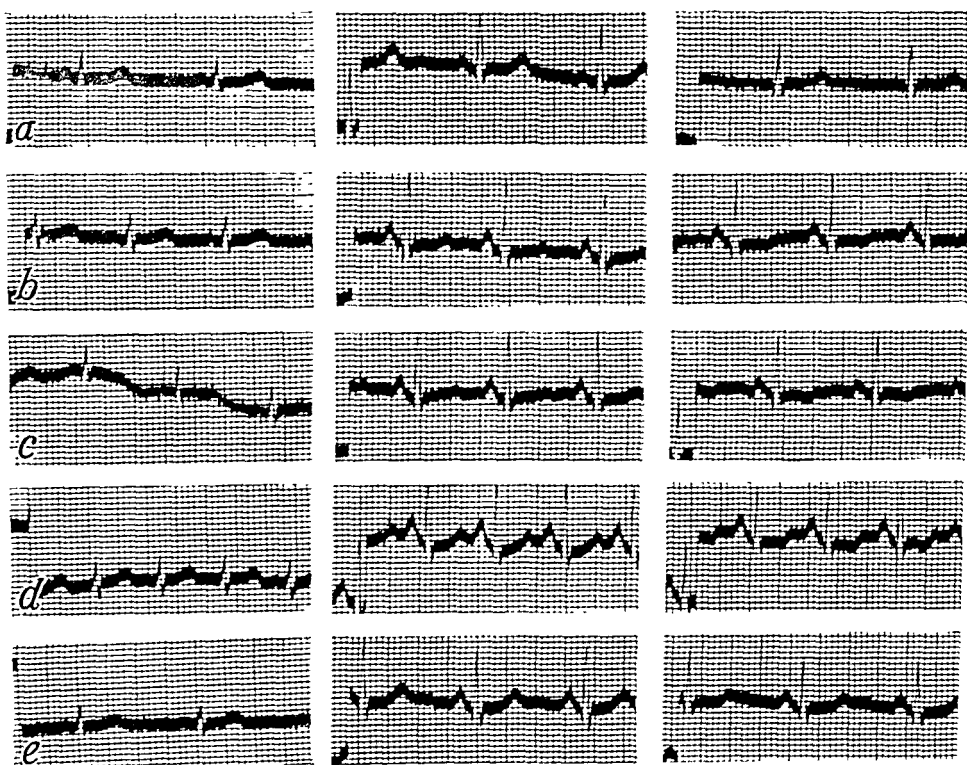


FIG. 2a-e.—a, Patient in the supine position; b, standing; c, after exercise while still standing; d, after nitroglycerine while standing; e, immediately on lying down.

In the first series of Figure 2 there is a normal electrocardiogram taken from a 26-year-old healthy young man. The *T*-waves are positive in all leads. The second series (Fig. 2b), taken after the patient stood 5 minutes, shows larger *P*-waves in Leads II and III, and smaller *P*-waves in Lead I. The *T*-waves are lower in Lead II and definitely inverted in Lead III. No marked changes appeared after exercise (Fig. 2c). Two minutes after the administration of $\frac{1}{100}$ gr. of nitroglycerine the rate increased from 90 to 110 per minute (Fig. 2d), the *S-T* segment became markedly depressed in Leads II and III, and the *T*-wave in Lead III became more inverted than

before. The fifth series (Fig. 2c) was taken immediately on lying down. The heart rate diminished to 80 per minute, the *T*-waves became normal, the *S-T* segments in Leads II and III are still slightly depressed as a result of the nitroglycerine. The inversion of the *T*-wave in Lead III which appeared in the erect position never disappeared after the administration of nitroglycerine.

From these results one may conclude that anoxia of the heart, as well as an insufficient blood supply, do not play any rôle in the formation of the described alterations of the *T*-waves. Since a change of position of the heart within the chest seemed the next most probable explanation of the alterations of the *T*-waves, we took electrocardiograms while the patient was recumbent, while standing, and then, while the patient was still standing, in full inspiration and expiration.

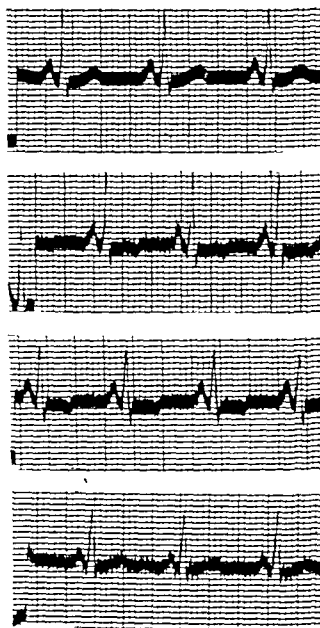


FIG. 3.—Lead II. First tracing, patient in the supine position; second, in erect position; third, during deep inspiration; fourth, during deep expiration, while still standing.

Figure 3 shows 4 electrocardiograms, each taken in Lead II. The first shows the normal tracing taken while the patient was supine; the second while he was standing. The formerly normal positive *T*-wave became inverted. The third tracing was also taken while the patient was standing, but during maximum inspiration. It shows increased inversion of the *T*-wave. Without a change of posture the patient was asked to exhale completely. The *T*-wave became immediately positive (fourth tracing).

Figure 4a shows a right axis deviation registered in a healthy

individual. The *T*-waves were positive in Leads I and II, and negative in Lead III. This negativity increased in Lead III when the electrocardiogram was taken while the patient stood (second

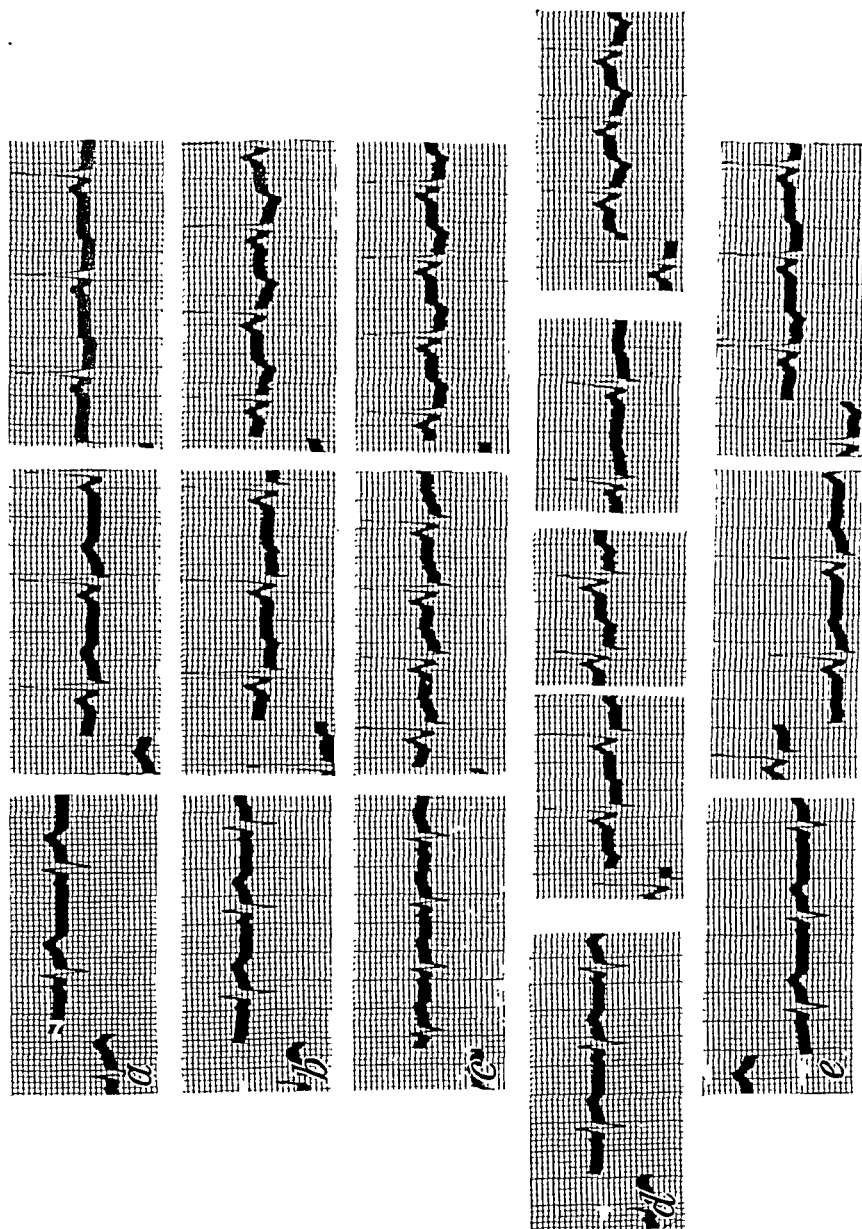


FIG. 4a-d.—*a*, Three limb leads with the patient lying flat; *b*, while standing; *c*, after exercise; *d*, after nitroglycerine, while still in the upright position. The second lead was taken in three sections; first, while the patient was breathing normally; second, during deep inspiration; third, during deep expiration; *e*, immediately after lying down.

series). The *T*-wave in Lead II also became negative. After exercise the *S-T* segment became slightly depressed (Fig. 4c), and the *T*-wave less negative. The administration of $\frac{1}{100}$ gr. of nitroglycerine increased the depression of the *S-T* segment and the negativity of the *T*-waves in Leads II and III (Fig. 4d). The electrocardiogram in Lead II was also taken in deep inspiration. It shows a marked increase in the negativity of the *T*-wave (third tracing in the fourth series). Then the electrocardiogram was taken in deep expiration with upward pressure of the diaphragm by means of a large rubber balloon (fourth tracing in the fourth series). The *T*-wave became isoelectric. Immediately after the patient lies down, the electrocardiogram (Fig. 4d) is almost normal. The slight tachycardia and depression of the *S-T* segment in Lead II are still the consequence of the nitroglycerine.

The electrocardiogram was examined in deep inspiration and expiration 15 times. In all but one case the *T*-wave became more inverted in inspiration, and much less inverted or normal in expiration combined with abdominal pressure as seen in Figures 3 and 4. In only one case (Fig. 5) were the changes exactly opposite; namely, higher *T*-waves in Lead III in inspiration, and inverted *T*-waves in expiration. In this case, however, there were also very marked changes in the initial complex. In the supine position this patient showed normal positive *T*-waves in Leads I and II; the *T*-wave in Lead III was low and preceded by a slightly depressed *S-T* segment (first series). In the upright position, the *S-T* segment in Lead III became more depressed (second series); during full inspiration (third series) the initial complex in Lead I became smaller and the *T*-wave in Lead III became positive. During expiration and abdominal pressure (fourth series) left axis deviation appeared, and the *T*-wave in Lead III became inverted. Immediately on the patient lying down, the electrocardiogram returned to normal.

Changes in the form of the *T*-waves in Lead III during deep respiration have been known to occur in the healthy. Scherf and Boyd¹⁷ described a case with a right axis deviation and a negative *T*-wave in Lead III in inspiration, and a left axis deviation and a positive *T*-wave in Lead III in expiration. Such marked changes are rare when the patient is recumbent. The quick and frequent change in the form of the *T*-waves in the third lead during respiration in the patient while standing is remarkable. From these tracings we may conclude that a rapid change in the position of the heart, as occurs during deep inspiration and expiration, may markedly influence the form of the *T*-waves in Lead III (and II).

Discussion. It has been pointed out that the inversion of the *T*-waves in Leads II and III in the standing patient cannot be regarded as a sign of a myocardial lesion. It is necessary to determine whether these changes are due to coronary insufficiency or anoxia of the heart (orthostatic anemia), or whether they are due to

mechanical, physical factors. At the outset there are a few arguments which speak against the assumption of an anoxia of the heart or parts of it. First, the form of the alterations of the final deflection deserve consideration. In the erect posture one usually finds only an inversion of the *T*-wave in Leads II and III, but rarely a marked depression of the *S-T* segment. Pronounced depression of the *S-T* segment, however, is characteristic of coronary insufficiency and a reduced blood supply to the heart. Changes of the *T*-waves alone are found only in very circumscribed cardiac damage such as in coronary occlusion, myocarditis, and so on. In the exercise test,⁶ or the anoxemia test^{12,15} the *S-T* segment is primarily altered.

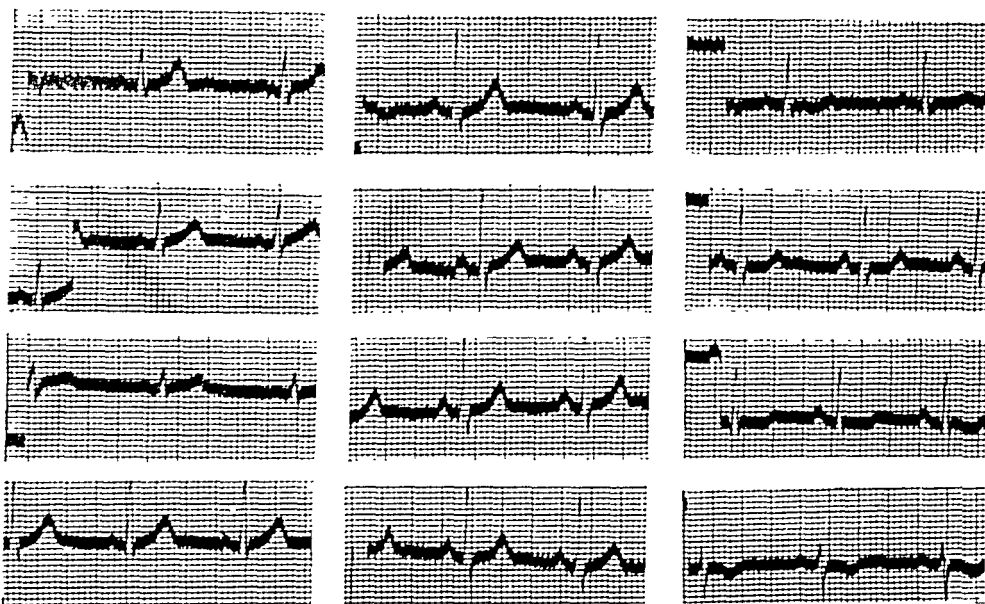


FIG. 5a-d.—a, Patient supine; b, erect position; c, during deep inspiration; d, during deep expiration, while standing.

Second, the alterations of the electrocardiogram in anoxia disappear slowly. It may even require as long as 30 minutes before the electrocardiogram will assume its usual form. The changes in the *T*-wave caused by a change of posture disappear immediately upon lying down. Third, a few minutes after the anoxia of the heart caused by physical effort in coronary stenosis subsides, frequently the *T*-waves are unusually high for a short time. This has been explained⁶ by a reactive hyperemia following diminished cardiac blood supply and anoxia. We never encountered these changes after the patient had been standing. Fourth, upon the assumption of an upright position the electrocardiogram never revealed an inversion of the *T*-wave in Lead I, which is a common event in general anoxia.

The result of the investigations reported in this paper show that change of position of the diaphragm in different phases of respiration in the standing patient causes marked alterations of the electrocardiogram to appear, and that the inversion of the *T*-wave, which develops when the patient stands, disappears in complete expiration; this speaks definitely against the assumption of any coronary insufficiency, myocardial damage, and so on. Furthermore, if anoxia were the cause of the changes described, then exercise should increase them and nitroglycerine should abolish them. However, just the opposite occurred. As is typical for the healthy heart and the heart without impairment of blood supply, the *T*-waves became higher on exercise, and lower following nitroglycerine. The latter effect may be due to the tachycardia and fall of blood pressure, both of which cause a diminished cardiac blood supply. It is also possible that the dilatation of large areas in the splanchnic field still further diminishes the myocardial blood supply. Furthermore, prolonged standing does not accentuate the changes. The results were the same whether the electrocardiogram was taken immediately on standing or after 12 minutes in this position. We could not confirm the findings of others¹⁸ who reported that the electrocardiogram taken immediately after standing showed less alteration than that taken a few minutes later, a fact which has been used as an argument in favor of an orthostatic anemia. The findings also bore no relationship to the blood pressure. The blood pressure might rise or fall slightly on standing, but the alterations were the same.

A diminished blood supply may play a rôle in cases of marked postural hypotension, as described by Sanders,¹⁶ but in our cases the blood pressure remained unchanged or did not change markedly during the alteration of posture. Obviously the findings must be physiologic and depend on posture and the position of the heart in the thoracic cage. The importance of the relationship between the heart and the diaphragm and other neighboring tissues in regard to the form of the *T*-wave has been pointed out.^{10,11,14,20} The assertion of different authors that the electrical axis of the main deflection frequently shifts to the right on standing while the axis of the *T*-waves shifts to the left (therefore a change of position cannot play a rôle),^{5,19} would be valid only for direct leads or under conditions of constant equal conduction of the electrical forces from the heart by adjacent tissues. This condition did not prevail in our investigations.

Since the electrocardiogram is frequently taken in the sitting position, even at present in some institutions, and since the *T*-waves in Leads II and III may become inverted under such circumstances,¹⁶ it is evident that at times serious errors may be made. We have frequently seen the diagnosis of posterior wall infarction made on the basis of an inverted *T*-wave in Leads II and III in the healthy individual. The report of "abnormal T-waves" in the healthy

young person, occasionally encountered in the literature,^{2,8} may be due to the fact that the electrocardiogram was obtained while the patient was sitting. These papers do not mention in which posture the electrocardiograms were taken, but in all such reports the *T*-waves were like those of patients who have been standing, namely, inversion in Lead III, less in Lead II, and never in Lead I.

Body build is an important factor in the production of the changes described above, since asthenic individuals more frequently show the inversion of the *T*-wave in Lead III.⁵

Since the appearance of inverted *T*-waves in Leads II and III when the examination is made with the patient erect is explained by a change of the position of the heart in relation to the neighboring tissues, particularly the diaphragm, it might be anticipated that the same changes would occasionally appear in a normal person while supine; this would occur if the heart happens to have a position similar to that of other persons when the latter are standing.



FIG. 6.—A 27-year-old healthy female while lying down; the upper tracing during normal respiration; lower, at the end of a deep expiration with her belt on.

Figure 6a was obtained from a 27-year-old woman who complained of palpitation, independent of effort. Physical examination revealed a short female, rather stocky in build with an unexpectedly small heart which was placed symmetrically in the midline and which barely touched the diaphragm. There was no evidence of an organic cardiac lesion. The electrocardiogram, recorded with the patient in the supine position, revealed low voltage in Lead I; the *T*-wave in Lead II was almost invisible and in Lead III it was inverted. These changes were identical with those noted in tracings of normal patients in the upright position.

The patient was asked to put on an abdominal belt for a moment; Figure 6b was taken during maximum expiration while the patient remained in the supine position. The *T*-waves became normally positive in Lead II and less inverted in Lead III.

Conclusions. The phenomenon of flattening or inversion of a formerly positive *T*-wave in Lead III in the upright position was studied in 35 patients. This inversion increased during deep inspiration and decreased at the end of maximum expiration with upward pressure on the diaphragm.

These observations speak against the assumption that cardiac damage or anoxia of the heart muscle can be the factor responsible

for the electrocardiographic alterations. They confirm the conception that the inversion of the *T*-wave is due to a change in posture, and therefore a change in contact between the heart and the neighboring tissues.

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FAT TOLERANCE TESTS IN PSORIASIS.

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IN recent years there has been a growing impression that there is an underlying disturbance in fat metabolism in psoriasis. In 1933, Grutz and Burger¹⁴ expressed the view that psoriasis is probably based on either of two possible explanations: 1. There may be a greater accumulation of fat in the blood than the skin is physiologically able to handle; this fat, being excreted from the blood through the skin capillaries, streams into the epidermis and produces the phenomenon of psoriasis. 2. Fats may be formed in unphysiologic structure or in incorrect proportions of their component fractions. These authors favored the first theory and most of the subsequent investigations are based on their work.

In an excellent review of theoretical, clinical, biochemical and therapeutic considerations in psoriasis, Gate, Chaniel, Vallet and Humbert¹⁰ noted:

1. The greater frequency of psoriatic lesions in otherwise healthy and well-nourished subjects; in individuals whose diets are especially

rich in proteins and fats; in winter when fats are taken in larger amounts. They mentioned the frequently noted decrease of psoriasis in Germany during the war years 1914-1918 which coincided with a very great curtailment in fat consumption. (It is apparent that the restriction was due to the shortage of butter, milk, cream, bacon and meats.)

2. The abnormally high content of lipoids in psoriasis scales.

3. The commonly reported disturbance in fat metabolism in psoriasis as shown by:

(a) Retention of lipoids in the blood.

(b) General elevation of the degree of lipemia.

(c) Frequent hypercholesteremia which some researchers consider as evidence of lipoid retention in general.

(d) Alimentary hyperlipemia.

4. The amelioration in psoriatic lesions, without local therapy, by methods intended to reduce hyperlipemia and hypercholesteremia, the best results being shown by a very low fat diet.

Most studies in alimentary hyperlipemia are based on the early observations of Flint⁷ in 1862, following which many investigators using various methods adequately demonstrated the rise in blood fats after fat feeding. As employed by Grutz and Burger,¹⁴ and practically all workers who studied their observations, the technique consisted in feeding 5 gm. of cholesterol in 100 gm. of olive oil and examining the cholesterol content of the blood at 4, 8, and 12 hour intervals. While it is true that no procedure based on the feeding of a large quantity of a single food substance can give an accurate picture of the organism's ability to handle that substance, in our opinion the method of Grutz and Burger represents a wider departure from average diet and normal physiology than is necessary. Since it is well known that the feeding of neutral fats will produce a rise in blood cholesterol,^{3,15,30} ingestion of cholesterol as part of the test fat meal is unnecessary. Furthermore, cholesterol is characteristic of animal fats,² being absent in vegetable fats; it is therefore more likely that a great increase in blood cholesterol will follow the feeding of animal fat. It is also noteworthy that in the average diet the bulk of the fats are of animal origin. While there is definite evidence to the contrary,³⁰ it has been stated that the changes in the total cholesterol of the blood after a fat meal are slight and inconstant.^{4a} This has led most students of the problem of fat metabolism in psoriasis to study only plasma cholesterol and cholesterol esters, disregarding the function of the free cholesterol contained in the red blood cells. Yet Knudson¹⁸ concluded that the red blood corpuscles play a very active part in fat metabolism.

It has been stated that a minimum of 3.5 gm. of fat per kilo of body weight is needed to produce consistently alimentary hyperlipemia.²² Boyd⁶ objected to this amount on the ground that it indicated an unphysiologic intake of 200 gm. of fat per meal.

We have accordingly used a procedure which more closely approximates the average diet. Other observers^{1,5a,b,8,11,26,31} have shown that this method, or some modification of it, definitely yields a frank rise in blood cholesterol. We have been able to produce alimentary hyperlipemia consistently by using in a test meal (to be described below) 100 gm. of fat. Such an amount is roughly comparable to the 1.75 gm. of glucose per kilo of body weight commonly used in sugar tolerance tests.

Most of the observers who studied fat metabolism in psoriasis collected blood samples at 4, 8, and 12 hour intervals after the fat meal. As Wechsler³³ has stated, "Even a cursory review of the literature indicates that a typical curve has not been obtained." We feel that in order to note even slight variations in blood constituents after a test meal an interval of much less than 4 hours is imperative. In our determinations the total cholesterol of whole blood was used as a measure of hyperlipemia.

Procedure. After a 12-hour fast a blood specimen was taken. The patient was then given 500 cc. of 20% cream, representing 100 gm. of fat. Blood specimens were obtained at intervals of $1\frac{1}{2}$, 3, $4\frac{1}{2}$, 6, and $7\frac{1}{2}$ hours and the whole blood was examined for total cholesterol by the method of Bloor.^{4b} During the time of the test the patient was allowed to take very occasional sips of water. Most of the patients were ambulant but activity was closely restricted.

Material Studied. In this investigation 10 patients with unequivocal psoriasis were studied (see Table 1). Of these, 6 were males and 4 were females. Their ages ranged from 22 to 75 years. The duration of their psoriasis varied from 2 to 40 years. The severity of the lesions varied from a few small discoid areas on the extremities to large, generalized areas distributed over the trunk and extremities. Two of the female patients (Cases 2 and 3) had each had 2 pregnancies. An arbitrary figure of 10% above or below average "normal" weight for age, sex, and height was used to determine whether the patient was obese or underweight. By these very narrow standards Case 2 was 24% and Case 8 was 10% overweight; Case 5 was 15% and Case 7 was 14% underweight. Excluding the obesity or underweight as already noted, none of these 10 patients had any complaints or abnormalities other than psoriasis, except Case 3 who had a small fibromyoma of the uterus.

As controls, 13 patients without evidence of past or present chronic skin disease were studied. Of these patients, 5 were males and 8 were females. Their ages ranged from 20 to 65 years. Seven patients were free of any apparent metabolic disturbance. Three patients (Cases 8, 9, 10) had well-controlled diabetes mellitus and 1 of these (Case 8) had in addition mild nephritis of the nephrotic type. There was 1 case of hyperthyroidism (toxic adenoma—Case 5), 1 of hypoparathyroidism (Case 11), and 1 of hypothyroidism (Case 13). The cases of diabetes mellitus and the thyroid

dyscrasias were especially included because of their well-known tendency to altered fat metabolism. By the same criteria as used for the psoriatic cases, Case 8 was 10% and Case 12 was 26% overweight; Case 1 was 12%, Case 5 was 24% and Case 7 was 16% underweight.

TABLE 1.—DATA ON CASES OF PSORIASIS AND NON-PSORIASIS.

Case No.	Age.	Sex.	Nude wt.	Normal wt.	<i>Psoriasis.</i>		Distribution of lesions.	Activity of lesions.	Duration in years.
					Over-wt., %.	Under-wt., %.			
1	75	M	145	135	7	..	Elbows, knees, back, groin	3+	40
2	47	F	173	139	24	..	Right knee and elbow	2+	27
3	34	F	128	124	3	..	Elbows, knees, left foot	3+	15
4	35	F	116	126	..	8	Elbows, knees, back, abdomen	4+	20
5	27	M	138	163	..	15	Elbows, knees	2+	2
6	22	F	108	116	..	7	Elbows, knees	2+	3
7	58	M	146	170	..	14	Elbows, knees, back, chest	4+	25
8	25	M	163	147	10	..	Elbows, chest, back	1+	4
9	22	M	139	136	2	..	Elbows, trunk	4+	4
10	55	M	143	150	..	4	Generalized	4+	30

Case No.	Age.	Sex.	Nude wt.	Normal wt.	<i>Non-psoriasis.</i>		Diagnosis.
					Over-wt., %.	Under-wt., %.	
1	26	M	149	171	..	12	Chief complaint: thinness; totally negative history and physical
2	35	F	132	127	4	..	Lumbosacral strain
3	20	F	113	121	..	6	Nephroptosis, irritable colon
4	32	F	117	122	..	4	Irritable colon
5	39	F	105	139	..	24	Hyperthyroidism
6	63	M	146	150	..	2	Duodenal ulcer
7	31	M	120	143	..	16	Healed pulmonary tuberculosis
8	48	F	148	134	10	..	Controlled diabetes mellitus, mild nephrotic type nephritis
9	52	F	150	139	7	..	Controlled diabetes mellitus
10	65	M	141	155	..	9	Controlled diabetes mellitus
11	54	F	142	143	Hypoparathyroidism
12	44	F	176	139	26	..	Hypertension
13	24	M	176	153	15	..	Hypothyroidism

Results. (See Table 2.) The fasting total cholesterol levels in 10 cases of psoriasis lay between 150 mg. and 312 mg. per 100 cc. of whole blood, the average being 192 mg. (Fig. 1). Only 1 patient revealed a fasting blood cholesterol above the highest commonly accepted normal level of 240 mg. per 100 cc. of blood (Case 10). This patient, however, had the most severe and most widely distributed psoriatic lesions. The degree of rise from fasting to the highest level of blood cholesterol varied from 31.9% to 108%, the average being 51.4% (Fig. 2). The highest level of blood cholesterol was attained in 1½ hours in 1 case or 10% of the cases, 3 hours

in 2 cases (20%), 4½ hours in 4 cases (40%), 6 hours in 2 cases (20%), and 7½ hours in 1 case or 10% of the psoriasis cases studied (Fig. 3).

In the 13 control patients the fasting total cholesterol ranged from 123 to 250 mg. per 100 cc. of whole blood, the average being 188 mg. (Fig. 1). The degree of rise from fasting to peak level ranged from 25% to 112%, the average rise being 62.8% (Fig. 2). The highest level of absorptive specimen was obtained in 3 hours in 2 cases (15.4%), 4½ hours in 9 cases (69.2%), and 6 hours in 2 cases (15.4%) (Fig. 3).

TABLE 2.—BLOOD CHOLESTEROL.

Psoriasis.

Case No.	Fasting.	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	7½ hrs.	Time of peak.	Change, %.
1	150	192	250	312	208	160	4½	108
2	151	160	192	...	208	160	6	37.7
3	160	208	217	227	192	184	4½	41.8
4	166	192	208	250	192	172	4½	50
5	166	178	200	217	227	217	6	36
6	166	185	...	208	178	150	4½	25
7	172	185	227	218	192	160	3	31.9
8	227	262	276	312	357	384	7½	68
9	250	454	312	250	208	192	1½	81
10	312	418	500	454	384	312	3	35

Non-psoriasis.

1	123	132	147	151	166	151	6	35
2	138	156	171	227	171	147	4½	64
3	147	166	192	227	178	151	4½	54
4	147	192	227	312	250	...	4½	112
5	166	192	208	192	166	147	4½	25
6	166	192	250	276	250	192	4½	66
7	189	227	250	263	238	208	4½	39
8	218	276	416	357	340	270	3	90
9	227	238	250	333	277	172	4½	47
10	250	317	416	272	250	147	3	66
11	250	268	272	416	333	238	4½	66
12	250	312	357	416	312	227	4½	67
13	171	...	208	250	312	288	6	82

Total blood cholesterol in mg. per 100 cc. of whole blood.

Time of peak (highest blood cholesterol) in hours after ingestion of test meal.

Per cent of change from fasting blood cholesterol to level at peak of curve.

It is striking that this study indicates that in psoriatic patients there is no significant departure from non-psoriatics in the ability to metabolize fats, as judged by the rate of absorption from the intestine and the rate of disappearance from the blood stream, the total cholesterol of whole blood being used as a criterion. In fact, the group of patients without dermatologic lesions showed slightly higher fasting levels and a somewhat greater degree of rise above the fasting levels than the group of psoriatic patients.

In both groups, particularly in the non-dermatologic patients, there appeared to be a tendency for the thinner patients to exhibit smaller degrees of rise of the fat tolerance curves, while the obese persons tended to show higher peaks (Table 3). This phenomenon was previously demonstrated by Blotner.^{5a,b}

Comment. It is common experience to find an elevation in the cholesterol and total fat of the blood in such conditions as nephrosis, hypothyroidism, diabetes mellitus, xanthomatosis or xanthelasma, and pregnancy. In xanthomatosis the cholesterol accumulates in

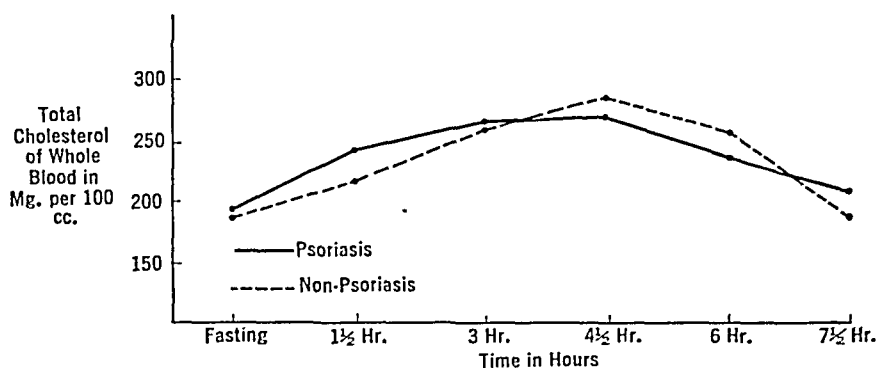


FIG. 1. COMPOSITE FAT TOLERANCE CURVES.

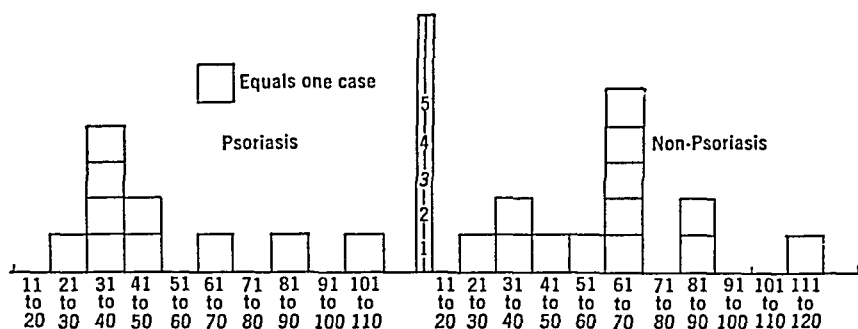


FIG. 2.—PERCENTAGE CHANGE FROM FASTING TO PEAK LEVEL OF BLOOD CHOLESTEROL.

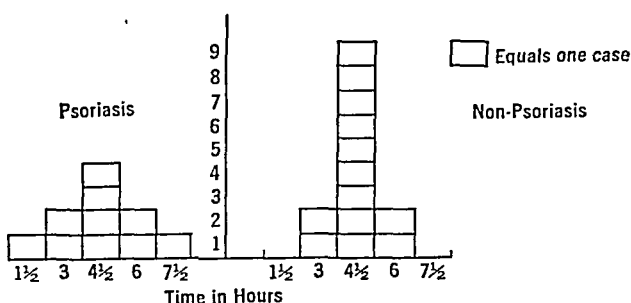


FIG. 3.—TIME OF HIGHEST BLOOD CHOLESTEROL LEVEL AFTER FAT TEST MEAL.

localized areas without disturbance of the epidermis or the most superficial layers of the skin. It is evident that the mere presence of hyperlipemia is not responsible for the production of lesions even remotely resembling those of psoriasis in this condition. In hypothyroidism even of advanced degree, where the skin is dry and scaly

and myxedema is marked, psoriasis is not a commonly observed feature. It has not been possible to find any reference in the literature to the regular coincidence of nephrosis and psoriasis.

Grutz and Burger¹⁴ point to the "simultaneous or alternate occurrence of psoriasis and diabetes." Although our series is small, it is noteworthy that in a recent experience covering 64 patients with diabetes mellitus on the service of Dr. Mitchell Bernstein at Jewish Hospital we have not noted the coincidence of this disease and psoriasis. In a review of 500 cases of diabetes mellitus Greenwood¹² found 12 cases of psoriasis (2.4%), an incidence too small to suggest close association between these two diseases. According to Sutton,²⁹ psoriasis constitutes between 2% and 3% of average clinical experience, showing that diabetes mellitus bears no special relationship to psoriasis since these figures parallel those of Greenwood.

TABLE 3.—COMPARISON OF DEGREE OF RISE OF BLOOD CHOLESTEROL LEVEL WITH DEGREE OF OBESITY OR THINNESS.

<i>Psoriasis.</i>				<i>Non-psoriasis.</i>			
Case No.	Over-weight, %.	Under-weight, %.	Change of cholesterol, %.	Case No.	Over-weight, %.	Under-weight, %.	Change of cholesterol, %.
6	..	7	25	5	..	24	25
7	..	14	31.9	1	..	12	35
10	..	4	35	7	..	16	39
5	..	15	36	9	7	..	47
2	24	..	37.7	3	..	6	54
3	3	..	41.8	2	4	..	64
4	..	8	50	10	..	9	66
8	10	..	68	11	66
9	2	..	81	6	..	2	66
1	7	..	108	12	26	..	67
				13	15	..	82
				8	10	..	90
				4	..	4	112

Arranged according to increasing degree of rise of blood cholesterol.

There is a physiologic increase in the cholesterol of the blood in the latter months of pregnancy. Not only is psoriasis a rare complication of pregnancy, but 2 of our patients (Cases 2 and 3) reported that during their pregnancies the psoriatic lesions improved progressively, only to recur some months after delivery. Numerous similar reports in the literature^{9,17,19-21,24,28} indicate that psoriatics in whom pregnancy supervenes usually show marked amelioration of the lesions, often to the point of complete clearing of the skin, with exacerbation either shortly after parturition or at the termination of lactation. Progressive local betterment in psoriatic pregnant women would seem to be the result of physiologic withdrawal of cholesterol from the tissues. The same reasoning can be applied to the effect of marked limitation of diet, whether for therapeutic purposes or as the result of qualitative and quantitative restriction of diet during war times. Starvation usually causes hyperlipemia affecting all the lipid constituents of the blood.²⁵ The improvement noted in the psoriatic lesions of patients maintained on diets

low in fats is by no means necessarily the result of an alteration in fat metabolism in the body as a whole. It is more likely the effect of mobilizing from all tissues essential substances, such as cholesterol, which are not being supplied by the diet. Marchionini, Manz and Huss²³ have shown that even in normal persons the skin lipoids are definitely influenced by fat feeding within a short time after the ingestion of a fat test meal. These authors have also demonstrated that the local effect varies according to the skin area examined. Removal of a substance from a tissue or area which cannot metabolize it normally should ameliorate local evidences of such faulty metabolism.

It is well known that the adrenal cortex not only is very rich in cholesterol and other lipoids⁷ but probably exerts a more profound and direct influence on these substances than any other gland or organ.^{16,27,32} In this connection should be noted the marked hypertrophy of the adrenal cortex which occurs physiologically during pregnancy.¹³ The striking improvement reported by Gruneberg¹³ in cases of psoriasis treated with adrenal cortical extracts or hypophyseal corticotropic hormone is apparently not specific in its local influence on the psoriatic lesions but more probably the result of the fat mobilizing action of the adrenal cortex, causing withdrawal of the lipoids from all tissues, including the skin.

Summary. Because of a growing tendency to attribute psoriasis to a generalized disturbance in fat metabolism, the fat tolerance was studied in 10 patients with this disease. Changes in the total cholesterol of whole blood were used as an index of the degree of alteration of the blood lipid level. The psoriatic subjects showed no significant changes as compared with 13 non-psoriatic patients acting as controls.

The incidence of psoriasis in conditions exhibiting hypercholesterolemia or hyperlipemia, such as hypothyroidism, diabetes mellitus, xanthelasma, nephrosis and pregnancy was reviewed. Only pregnancy has a relationship to psoriasis and that influence is distinctly beneficial.

The amelioration of psoriasis in starvation, low fat intake, pregnancy and in individuals receiving adrenal cortical extract or hypophyseal corticotropic hormone is, in our opinion, the result of the mobilization of fats and lipoids from all the tissues. This removes locally, from the skin, substances whose presence is irritating.

Conclusions. We believe that it is reasonable to conclude from our studies herein presented that psoriasis is a disease due to conditions existing locally in the skin. It is possible that a generalized disturbance in fat metabolism may contribute to such local conditions. However, we have not been able to demonstrate in fat tolerance tests with more closely spaced blood samples than have heretofore been employed that such a generalized disturbance exists.

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URINARY EXCRETION OF SULFAPYRIDINE IN THE RAT.

A RELATIONSHIP OF THE LIVER TO UROLITHIASIS.

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SULFAPYRIDINE, like sulfanilamide, is excreted in the free and acetylated form in the urinary tract of man (Baines and Wien,² Ratish, Bullowa, Ames, and Scudi,¹³ Marshall, Bratton, and Litchfield¹¹). Unlike acetylsulfanilamide, acetylsulfapyridine is highly insoluble and urolithiasis has been found to result from the deposition of this substance in the urinary tracts of certain patients and experimental animals (Antopol and Robinson,¹ Gross, Cooper, and Lewis,⁵ Long and Wood¹⁰). Preliminary studies (Ratish, Bullowa, Ames, and Scudi,¹³ Scudi, Ratish, and Bullowa¹⁶) have indicated the presence of unidentified soluble excretion products in human urine following the administration of sulfapyridine. Recently it was announced

(Scudi¹⁴) that a hydroxysulfapyridine* and its very water-soluble glucuronide were isolated from dog urine. Since the dog does not acetylate the drug, rats were used in the present study because this animal, like man, excretes the drug in both the free and acetylated forms.

Experimental. White rats, weighing 175 to 225 gm., were placed in small metabolism cages in groups of 3 and kept on a diet of purina pellets and water *ad libitum*; in addition, 3 cc. of water per 100 gm. of body weight were given daily by stomach tube. Urine was collected over 24-hour periods and the volume and glucuronic acid content (Maughan, Evelyn, and Browne¹²) were measured. This experiment was repeated for 2 days with each group to measure the average daily output of glucuronic acid for control purposes. The animals were then given 1 gm. of sulfapyridine in aqueous suspension per kilo. body weight, daily for 12 days. Daily samples of urine were analyzed for free and acetylsulfapyridine (Bratton and Marshall³) as well as for glucuronic acid. Certain clinical reports have indicated a higher incidence of uroliths in children than in adults (Tsao, McCracken, Chen, Kuo, and Dale¹⁵). For this reason, 5 groups (5 animals per group) of young rats were similarly studied. The drug was suspended in 10% acacia and administered by stomach tube to a third series of 8 groups of rats, other conditions being maintained as in Series 1 and 2. Since gum acacia is a source of glucuronic acid, 2 additional groups of animals were given equivalent amounts of gum acacia and the daily glucuronic acid output was measured, but no increase beyond the norm was noted during a 2-week period.

In the interests of space only the results obtained in the third series of experiments are recorded (Table 1). Essentially the same results were obtained in the two previous series. The data indicate that sulfapyridine augments the glucuronic acid output. When groups of these animals were no longer fed sulfapyridine, their glucuronic acid output fell to normal, and upon readministration of the drug, the glucuronic acid was again increased.

Since appreciable variations occurred in the findings, the food intake was controlled more rigorously in another group of animals as follows: Each of 24 animals (3 rats per group) was given 3 cc. of a mash (50 gm. of 100 mesh purina chow per 115 cc. of water) per 100 gm. body weight 3 times daily. Bodyweight, water consumption, and urine volumes were measured daily. These did not vary significantly. After a control period of 5 days, during which the daily glucuronic acid output was measured, sulfapyridine (1 gm. per kilo.) was administered daily for 7 days and the urine was analyzed for glucuronic acid (Maughan, Evelyn, and Browne¹²), free sulfapyridine, and acetylsulfapyridine (Bratton and Marshall³).

During the first few days of sulfapyridine administration, there is no constant ratio between the urinary free and acetylsulfapyridine, as shown in Chart 1. The daily acetylsulfapyridine output reaches a reasonably constant level 24 hours after the first dose of the drug.

* This product is of interest in connection with redox theories of the mode of action of the sulfanilamide series of drugs.

After the fourth day a fairly constant output of free sulfapyridine is attained. The ratio is then approximately 3.5 to 1 at the dose level studied. This ratio is almost twice as great as the solubility ratio (2 to 1) of free and acetylsulfapyridine. Assuming saturation of the urine, 40% of the "free" sulfapyridine may be present in a soluble form. Maximal output of free sulfapyridine occurs on the 4th day following initiation of sulfapyridine administration (Chart 1), whereas maximal output of glucuronic acid occurs on the 5th and 6th days (Chart 2). A similar parallelism is shown in Table 1.

TABLE 1.—GLUCURONIC ACID OUTPUT IN MG./100 GM. BODY WEIGHT.

Group:	1	2	3	4	5	6	7	8
Average wt. per group:	664	795	774	582	662	494	533	670
<i>Day</i>								
1 . . .	8.7	8.6	8.2	11.3	9.3	6.7	8.6	8.4
(normal)								
2* . . .	7.8	8.5	9.9	12.0	11.1	6.6	9.4	7.3
(normal)								
3 . . .	14.3	13.6	15.0	19.2	18.6	7.1	15.0	15.5
4 . . .	19.7	13.5	17.8	25.6	17.7	7.5	18.2	13.2
5 . . .	30.8	24.2	12.5	20.2	19.1	16.3	22.3	19.4
7 . . .	18.5	20.4	9.9	23.6	15.6	21.8	19.8	15.5
15 . . .	11.9	19.0	16.9	12.4	19.6	14.2	8.1	
<i>Free Sulfapyridine.</i>								
3 . . .	18.1	12.1	13.2	24.6	19.4	5.9	10.6	11.6
4 . . .	22.6	13.9	16.3	23.6	21.5	4.7	15.4	12.4
5 . . .	26.0	24.9	14.8	28.4	25.5	12.5	24.4	19.0
7 . . .	25.4	26.0	21.5	31.3	23.0	21.3	25.3	15.5
15 . . .	24.7	37.6	29.5	32.5	40.2	35.3	31.2	
<i>Acetyl Sulfapyridine.</i>								
3 . . .	13.6	10.6	13.6	16.3	16.6	5.3	8.3	9.6
4 . . .	18.1	13.2	16.3	18.4	16.6	5.3	8.6	9.4
5 . . .	13.7	10.8	6.8	13.7	12.5	9.3	25.1	12.5
7 . . .	16.2	14.9	6.5	19.4	14.4	19.5	16.1	7.0
15 . . .	4.1	7.0	7.3	6.7	6.0	7.0	3.3	

* After the normal values were obtained, the animals were given 1 gm. per kilo. per day of the drug throughout the test period.

The influence of sulfanilamide and sulfathiazole upon the glucuronic acid output was similarly studied. Sulfanilamide, fed for 10 days, did not cause an increase beyond the normal level in 6 rats. Thus, at this dose level (1 gm. per kilo. per day), sulfanilamide is not excreted to any appreciable extent as a glucuronide. This does not eliminate the possibility of ethereal sulphate formation (Shelswell and Williams¹⁷). Sulfathiazole, similarly fed to 6 rats over a 10-day period, was intermediate between sulfanilamide and sulfapyridine in its effect upon the glucuronic acid output. This may indicate that part of the "free" sulfathiazole is excreted both as an ethereal sulphate and as a glucuronide.

Since the conjugation of an aglucone is a function of the liver, the following experiments were performed in order to study the effect of liver injury. Four groups of rats were given 0.35 cc. of chloroform in 0.5 cc. of sesame oil subcutaneously daily for 3 days. Three days after the last dose of chloroform, the animals were studied as previously. The results showed that the daily administration of sulfapyridine no longer caused an increase in the glucuronic acid output during the first 4 days of the experiment. After this time the

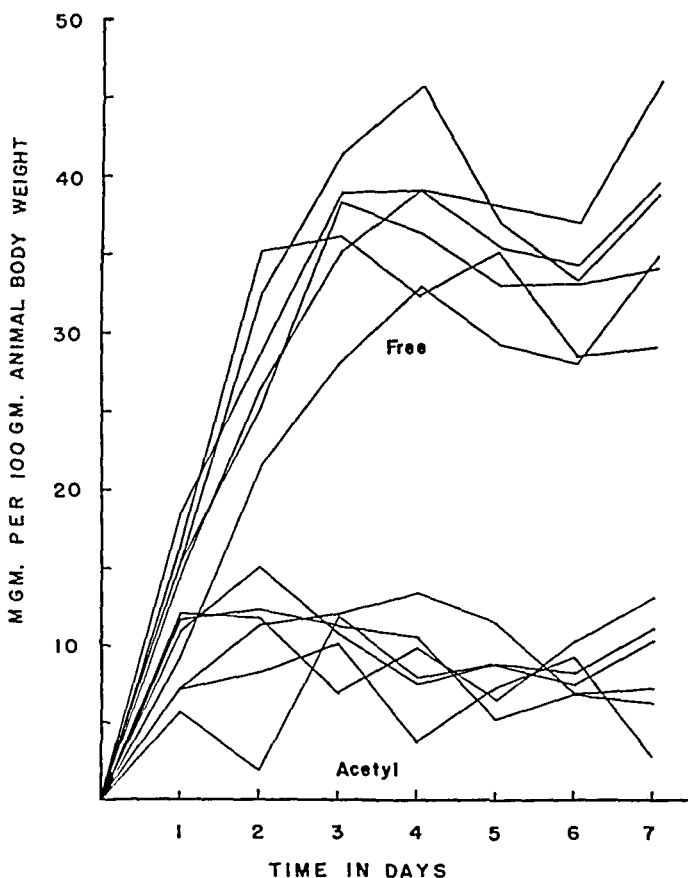


CHART. 1.—The daily urinary output of free and acetyl-sulfapyridine following the administration of 1 gm. of the drug per kilo. body weight of rat. Each line represents the results obtained with a group of 3 rats.

output began to show an upward trend, indicating a restoration of liver function. This is an agreement with the findings of Bueding and Ladewig⁴ who observed histologic evidences of liver regeneration following chloroform poisoning.

More severe and lasting liver damage was then produced in 12 rats by the subcutaneous injection of 0.75 mg. of yellow phosphorus in olive oil per 200 gm. of rat. These rats were fed 3 times daily by stomach tube. Body weights remained constant throughout the

test period. Water intake and urine volume did not deviate from the normal. The daily output of glucuronic acid remained essentially unchanged, and was not stimulated by the daily administration of 1 gm. of sulfapyridine per kilo. body weight. In 9 rats the output of free and acetylsulfapyridine was essentially equivalent to that observed in animals not treated with phosphorus. In 3 rats, however, the free and acetylsulfapyridine output was markedly depressed, but extensive concretions of acetylsulfapyridine were found in the kidneys of these animals whereas none were found at autopsy in the other 9.

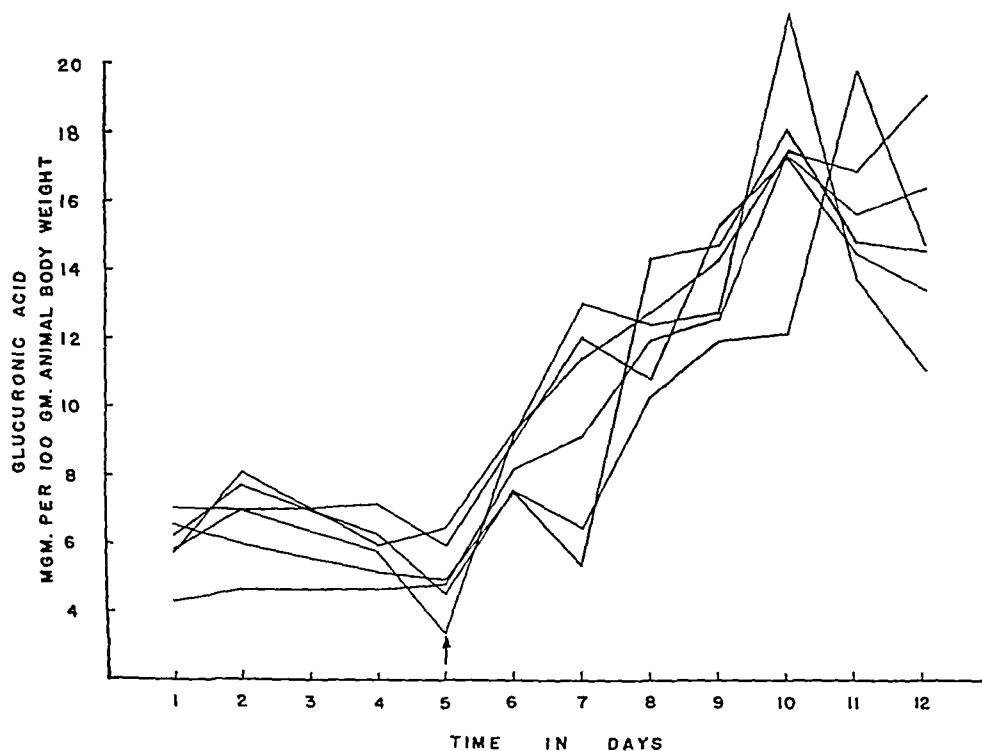


CHART 2.—The daily output of glucuronic acid. Each line represents the results obtained with a group of 3 rats. One gram of sulfapyridine per kilo. body weight was administered on the 5th and each succeeding day.

In order to decide if a still more severe liver damage would increase the incidence of urolithiasis, 20 rats were subcutaneously injected with 0.75 mg. of yellow phosphorus in olive oil, daily for 3 days. The animals were given 1 gm. of sulfapyridine per kilo. per day for 10 days and food and water were given *ad libitum*. Necropsy at the end of this time showed a 60% incidence of acetylsulfapyridine uroliths. These concretions contained 3.5% of the sulfapyridine in an unacetylated form. Thus, the stones are like those obtained without phosphorus poisoning. At this dose level only a 10% incidence of stones was found in a control series of 30 animals which were not treated with phosphorus. A 25% incidence was observed

in the series of 12 rats, mentioned above, following a single injection of phosphorus.

Discussion. It appears that the following steps, at least, are involved in the detoxication and urinary excretion of sulfapyridine. Sulfapyridine is, in part:

1. Excreted unchanged.
2. Rapidly acetylated in the liver and excreted as acetylsulfapyridine.
3. Oxidized in the liver to a hydroxysulfapyridine, some of which appears in the urine.
4. Conjugated with glucuronic acid in the liver after oxidation to hydroxysulfapyridine. This soluble product appears in urine.

Klein and Harris⁸ have studied the acetylation of sulfanilamide by the liver. Sulfapyridine is acetylated by cat liver and spleen (van Winkle and Cutting¹⁹). In the rat this detoxication is a relatively rapid reaction, since at a fixed dose level the daily output of acetylsulfapyridine reaches its maximum within the first 24 hours (Chart 2). On the other hand, excretion of the hydroxysulfapyridine glucuronide is a two-step procedure, requiring oxidation to the phenol and subsequent conjugation. In agreement with the findings of Lipschitz and Bueding,⁹ we find this over-all reaction (Chart 1) to be slow. At the present time our method* for the determination of the hydroxysulfapyridine is not sufficiently precise to permit a decision as to which of these steps is the rate controlling reaction.

Harris and Michel⁷ noted a difference in the time of occurrence of sulfanilamide and methemoglobin maxima in the blood and concluded that this lag in methemoglobin formation was "due to the time necessary for the formation and accumulation of sufficient quantities of the active agent." Comparison of Figures 1 and 2 in the present study shows that maximal free sulfapyridine output occurs on the 4th day following the initiation of sulfapyridine administration, whereas maximal glucuronic acid output occurs on the 5th and 6th days. This lag can be explained on the basis of a preliminary oxidation of the drug to the hydroxysulfapyridine. That such a reaction may occur in the liver was indicated by Harris⁶ and by our studies of liver damage. After the hydroxysulfapyridine is formed, it is then conjugated in the liver (Lipschitz and Bueding,⁹) and excreted by way of the urinary tract as the highly soluble hydroxysulfapyridine glucuronate.

In the absence of an accurate method for the determination of free and conjugated hydroxysulfapyridine, no precise estimate of the amounts of these substances present in urine can be given. There can be no doubt, however, that these substances do occur in rat urine in appreciable amounts. If one may assume that the increased urinary glucuronic acid is bound to a hydroxysulfapyridine, then

* This method involves an indophenol reaction similar to that used in the determination of vitamin B₆ (Scudi, Koones and Keresztesy¹⁶).

from stoichiometric considerations, as much as 40% of the "free" sulfapyridine may be excreted in urine in a soluble form.

Any means which may be employed to increase the percentage of the drug excreted in a water-soluble form should decrease the probability of urolithiasis. On the other hand, any dysfunction which appreciably decreases the percentage of the drug excreted in a soluble form may augment the possibility of urinary concretions; for example, in the present study phosphorus damage of the liver did not appreciably impair the ability of this organ to acetylate the drug, but it did inhibit the chain of reactions yielding the soluble product. The ability of the liver to conjugate the drug in a soluble form would therefore appear to be important. It may be desirable to test this function when occasion permits, and when prolonged sulfapyridine therapy is contemplated.

Summary. The urinary excretion of sulfapyridine has been studied in the rat. It has been shown that the drug augments the glucuronic acid output. Considering previous isolation studies in the dog, it is assumed that this indicates an *in vivo* oxidation of the drug to a monohydroxysulfapyridine with subsequent conjugation of glucuronic acid.

At the dose level used, it is estimated that as much as 40% of the free sulfapyridine may be present in the form of a highly soluble glucuronate.

Sulfanilamide does not stimulate the glucuronic acid output; sulfathiazole is intermediate between sulfanilamide and sulfapyridine in this respect.

Liver damage by phosphorus poisoning has been shown to prevent the increase in glucuronic acid output following sulfapyridine administration. The incidence of uroliths has been increased from 10 to 60% by phosphorus poisoning. Thus, in the rat the damaged liver is an important etiologic factor in urolithiasis.

The assistance and coöperation of Messrs. Otto Graessle and Joseph Mayner is gratefully acknowledged.

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SULFATHIAZOLE IN THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN.*

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SINCE sulfathiazole—the thiazole analogue of sulfapyridine—has recently been offered to the medical profession, the authors have felt that their experiences with drug in the treatment of pneumonia in infants and children should be recorded at this time. In doing this, no attempt will be made to review in detail the comprehensive chemical, bacteriologic, pharmacologic, chemotherapeutic and clinical studies which have already been published. These investigations have revealed that sulfathiazole is rapidly and regularly absorbed from the gastro-intestinal tract. Once absorbed, the drug is not conjugated (acetylated) as much as sulfapyridine, thus permitting a large proportion of it to be therapeutically active. Excretion of sulfathiazole is, however, rapid and this shortens the period of therapeutic efficiency. Nevertheless, the drug can be given often enough so that there is a pronounced and satisfactory influence on infections due to staphylococci and pneumococci.

TABLE 1.—LOCATION OF THE PNEUMONIA IN THE 77 PATIENTS TREATED WITH
SULFATHIAZOLE.

Part of lung involved.	No. of cases.
Right lower lobe	29
Left lower lobe	18
Right upper lobe	16
Left upper lobe	2
Right middle lobe	1
Left parahilar	4
Right parahilar	1
Left broncho-pneumonia (pneumococcus infection)	2
Bilateral pneumonia	3
Right upper and lower lobe	1
	<hr/> 77

In order to establish a dosage schedule for infants and older children, most of the patients admitted to the Pediatric Service of this hospital with a diagnosis of pneumonia were given sulfathiazole. Since the drug is poorly soluble it was administered by the oral route. During the 6-month period from January to July, 1940, 77 cases were observed. The diagnosis of the lung infection was made on the basis of a complete history, physical examination and roentgenogram study. The latter was a part of the admission procedure. Many of the patients came into the hospital close to

* Sulfathiazole was supplied by the Winthrop Chemical Company, Inc., New York.

the onset of disease. Twenty-seven cases had no physical findings over the chest at the time of admission. In these instances, the roentgenograms revealed very clearly the pneumonia. The distribution of the pulmonary involvement in our 77 children appears in Table 1, p. 718.

Before the sulfathiazole was administered the urine and blood of each patient was examined. This was followed by the bacteriologic study. An attempt was made to type all the cases employing the Neufeld method whenever pneumococci were found. Sputum specimens were usually obtained by aspiration with a bulb. When any difficulty occurred with this procedure, gastric specimens were used for typing. Occasionally, the latter specimens were so contaminated that the typing was not satisfactory. The distribution of the pneumococcus types among the patients treated with sulfathiazole is revealed in the following table:

TABLE 2.—THE PNEUMOCOCCUS TYPES IN THE 77 INFANTS AND CHILDREN WHO RECEIVED SULFATHIAZOLE.

Types.	No. of cases for each age period.					Total.
	Below 1 yr.	1-3 yrs. (incl.).	4-6 yrs. (incl.).	7-9 yrs. (incl.).	10-12 yrs. (incl.).	
<i>Mixed types:</i>						
V, XIV					1	1
I, XXXII			1			1
I, XVI, XVIII, XIX			1			1
VII, XX, XXIV			1			1
III, XVII		1				1
V, X		1				1
<i>Single types:</i>						
I	1	1	3	2	2	9
III		2	2			4
V		1	1	4	1	7
VI		3		2		5
VII			3	2		5
VIII				1	2	3
XIV	1	1	3		1	6
XVI	1	2				3
XIX	2	2	1			5
XX	2					2
XXI		2				2
<i>Untyped</i>	3	2	9	3	3	20
						<hr/> 77

Various doses of sulfathiazole were tried. The first group of cases of pneumonia received 2 to 3 gr. of the drug per pound of body weight (0.3 to 0.45 gm. per kilo) a day in divided doses for a period of 24 to 48 hours or until the temperatures dropped to normal; then the dose was reduced to $1\frac{1}{2}$ gr. per pound (0.22 gm. per kilo) and continued until the patients were free of fever for 72 hours. This usually required 3 to 5 days of drug therapy.

A subsequent group of children was given $1\frac{1}{2}$ gr. of the sulfathiazole per pound of body weight (0.22 gm. per kilo) a day in divided doses for the first 48 hours and then with a drop in the temperatures to

normal, this dose was reduced to 1 gr. per pound (0.15 gm. per kilo). Five to 7 days later the drug was discontinued. Since it now appeared that a dose of 1 gr. per pound per day might take care of the majority of the pneumococcus pneumonias in infants and children, the next series of cases admitted to the hospital received this dose. It was administered in divided doses, or every 4 hours, 6 times in 24 hours, and continued without any reduction until the temperature had been normal for 3 days. The total period of drug therapy was 5 to 6 days.

All ages were fairly well represented in each of the groups as will be noted in the following table:

TABLE 3.—VARIOUS AMOUNTS OF SULFATHIAZOLE EMPLOYED IN THE TREATMENT OF THE CHILDREN WITH PNEUMONIA.

Total dose per day based on body weight.	No. of cases for each age period.					Total.
	Below 1 yr.	1-3 yrs. (incl.).	4-6 yrs. (incl.).	7-9 yrs. (incl.).	10-12 yrs. (incl.).	
2-3 gr. per lb. (0.3-0.45 gm. per kilo.)	3	11	8	5	2	29
1½ gr. per lb. (0.22 gm. per kilo.)	3	3	5	3	2	16
1 gr. per lb. (0.15 gm. per kilo.)	4	4	12	6	6	32
						<hr/> 77

The patients were closely observed once the administration of the sulfathiazole had been started. Physical examinations were frequently made. After 48 hours of drug therapy or at the time of the first evidence of a critical fall in temperature, blood was drawn for a morphologic study and for a determination of the free sulfathiazole content. Roentgenograms were also taken. The whole procedure was usually repeated on the first day of normal temperature and again on the last day of the drug therapy. Repeated urinalysis were made on all the patients.

The response to the sulfathiazole therapy was most encouraging. The children took the drug well. Although there were a few instances of nausea, there was no vomiting. The drug was administered to infants by giving the powder produced from crushing tablets, with fruit juice or milk and feeding by a teaspoon, and to children by the same method, or by giving the tablet whole with small quantities of sweetened fluids. Occasionally liquids were not satisfactory, and in these cases foods such as flavored gelatin, sweetened fruit sauces, mashed banana, simple desserts or cereal with plenty of sugar were employed.

Twenty-nine children received an initial dose of 2 gr. or more per pound of body weight per day of the sulfathiazole. Within 24 hours after the drug was started, 21 (72% of the cases) had a critical drop in temperature and 17 (60% of the patients) had a normal temperature. At the end of 48 hours, all but 1 of the children had had a critical fall in temperature and 27 (93%) had a normal temperature

(Table 4). The free sulfathiazole level of the blood determined by the method of Bratton and Marshall ranged between 10 and 15.3 mg. per 100 cc. (Table 5).

Sixteen were given an initial dose of $1\frac{1}{2}$ gr. of the drug per pound of body weight per day. At the end of 24 hours, 9 (56%) of the patients had a critical drop in temperature and 8 (50%) of the cases had a normal temperature. Within 48 hours after the sulfathiazole was started, the fever had disappeared in all of the children (Table 4). The level of the drug in the free state in the blood varied from 3.7 to 14.1 mg. per 100 cc. (Table 5).

Thirty-two children received an initial dose of 1 gr. of the sulfathiazole per pound of body weight per day and this dosage was not decreased at any time during the period of drug administration. Within 24 hours after the drug was started, 23 (72%) of the cases had a critical fall in temperature and 17 (53%) of the patients had a normal temperature. At the end of the 48-hour period, 30 children had had their critical drop in temperature and 27 (85%) had a normal temperature (Table 4). The level of the drug in the free state in the blood varied from 4.6 to 10.3 mg. per 100 cc. (Table 5). Usually the pulse and respiration rates came down to normal figures shortly after the drop in temperature.

TABLE 4.—THE EFFECT OF SULFATHIAZOLE THERAPY ON TEMPERATURE.
The various total doses per day based on body weight.

	2-3 gr. per lb. (0.3-0.45 gm. per kilo.).		1½ gr. per lb. (0.22 gm. per kilo.).		1 gr. per lb. (0.15 gm. per kilo.).	
	No.	%.	No.	%.	No.	%.
Critical fall in temperature:						
Within 24 hours	21	72	9	56	23	72
Up to 48 hours	28	96	16	100	30	94
At end of 72 hours	29	100			32	100
Temperature at normal level:						
Within 24 hours	17	60	8	50	17	53
Up to 48 hours	27	93	16	100	27	85
At end of 72 hours	29	100			32	100
Secondary rise in temperature in 10 children (13%) . . .	3	4	2	3	5	6

TABLE 5.—AMOUNT OF FREE SULFATHIAZOLE IN THE BLOOD AS DETERMINED BY THE METHOD OF BRATTON AND MARSHALL.

Total dose per day based on body weight.	No. of cases.	Range of drug in mg. per 100 cc.
2-3 gr. per lb. (0.3-0.45 gm. per kilo.)	29	10.0 to 15.3
1½ gr. per lb. (0.22 gm. per kilo.)	16	3.7 to 14.1
1 gr. per lb. (0.15 gm. per kilo.)	32	4.6 to 10.3

The drug was administered every 3 or 4 hours throughout the day and night. Some of the children received soda bicarbonate with each dose of the sulfathiazole but the majority did not. Two children who were considered to be in acidosis at the time of admission to the hospital were given fairly large amounts of the alkali. Sedatives and cough mixtures were occasionally permitted. Serum therapy was not employed in any case.

The careful clinical observations of the patients together with the frequent roentgenogram examinations revealed that the resolution of the pneumonic infection began about the third or fourth day, was usually under way to a fair degree by the fourth or fifth day, was quite well advanced by the fifth to the sixth day, and in some cases completed by the seventh to eighth day. The critical drop in temperature preceded the beginning of resolution by 12 to 24 hours. Ten children (13%) had a secondary rise in temperature following the initial fall. In these children, resolution did not begin until the temperature had finally returned to normal.

No evidence of urinary disturbance was detected in any of the patients. The most disturbing feature of the chemotherapy was the appearance of a drop in the polymorphonuclear blood cells. This occurred in 10 cases listed in Table 6 beginning usually after the sulfathiazole had been administered for 48 hours and continued for 3 to 5 days. With a discontinuance of the drug, the white blood cells immediately began to rise, often reaching the normal figure in 7 days. No instance of a serious blood change was noted.

TABLE 6.—THE 10 CASES REVEALING ACUTE LEUKOPENIA WITH GRANULOCYTOPENIA.

Age.	Dose per day based on weight.		Actual amt. of drug received by each patient.		Admission counts.		Subsequent counts.	
	Gr. per lb.	Gm. per kilo.	Gr.	Gm.	White blood cell.*	Pmn. diff.†	White blood cell.*	Pmn. diff.†
3 yrs.	2	0.30	255	17	20000	80	5350	39
6 yrs.	2	0.30	390	26	20090	80	6000	20
8 mos.	1½	0.22	225	15	13000	50	5350	11
13 mos.	1½	0.22	153	10	12350	50	9850	20
3 yrs.	1½	0.22	225	15	9450	79	5500	29
3 yrs.	1½	0.22	150	10	7000	43	8800	31
3 yrs.	1½	0.22	142	9	6500	71	6450	29
4 yrs.	1½	0.22	262	17	29750	79	6102	29
9 yrs.	1½	0.22	626	42	6450	..	3400	35
5 yrs.	1	0.15	240	16	19850	85	4200	40

* Total white blood corpuscle count.

† Polymorphonuclear cell count based on 300 cells and expressed in %.

The incidence of complications was small. There was 1 case which developed empyema and another was found to have a lung abscess. The progress in each of these children was good. There were no deaths—all of the 77 children with type specific pneumococcus pneumonia or lobar pneumonia with negative typing receiving the sulfathiazole survived. These results equaled those of sulfapyridine and certainly surpassed those of specific serum therapy as may be observed in Table 7, p. 723.

Incidentally, the poor showing of the serum-treated cases was due to an insufficient dose of the specific serum, mistakes in typing, or infection by more than one type of the pneumococcus.

Sulfathiazole compares favorably with sulfapyridine. The latter drug acts faster as evidenced by the critical fall in temperature within 24 hours, although at the end of 48 hours the effect of both

drugs on the temperature was practically the same. Much of the nausea and vomiting which occurred frequently with the administration of sulfapyridine was absent when sulfathiazole was given. In fact, we had few untoward effects from the sulfathiazole. There was no vertigo, headache, and malaise. Fever and cutaneous eruptions were not observed, although these side effects have been seen by some investigators. Hematuria and anuria were not present. There was no evidence in any case of injury to nerve tissue. However, acute leukopenia with granulocytopenia did occur and cleared up soon after the sulfathiazole had been discontinued.

TABLE 7.—RESULTS OF THE TREATMENT OF PNEUMONIA (PNEUMOCOCCUS OR LOBAR) IN INFANTS AND CHILDREN AT THE MINNEAPOLIS GENERAL HOSPITAL DURING A CORRESPONDING PERIOD (JANUARY TO JULY) OF EACH YEAR.

Year.	No. of cases.	Treatment.	No. of cases of empyema.	% of empyema.	No. of deaths.	Mortality rate.
1933	69	No specific therapy	1	1.44	11	15.94
1934	75	No specific therapy	14	18.66	5	6.66
1935	86	No specific therapy	15	17.44	6	6.97
1936	138	Serum	14	10.14	9	6.52
1937	82	Serum	6	7.31	4	4.87
1938	68	Serum	2	2.94	10	14.70
1939	65	Sulfapyridine	3	4.61		
1940	77	Sulfathiazole	1	1.29		

We recommend sulfathiazole for the treatment of pneumonia in infants and children, although each patient must be closely watched for toxic reactions. Various amounts of the drug have been tried and it was found that 1 gr. per pound (0.15 gm. per kilo) was effective but that $1\frac{1}{2}$ gr. or even 2 gr. could be administered without any serious untoward effects. Sulfathiazole is supplied in tablets of 0.5 gm. (7.72 gr.) and also in tablets of 0.25 gm. (3.86 gr.). Although it would be ideal to determine the dosage requirements in the metric system, that is, the number of grams per kilogram per day, many practising physicians prefer to know the number of tablets necessary for each dose based chiefly on the age of the patient. For their convenience may we present the following schedule in which the doses are calculated on the basis of 1 to $1\frac{1}{2}$ gr. per pound (0.15 to 0.22 gm. per kilo) of average body weight per day. The sulfathiazole should be administered without any reduction every 4 hours, 6 times in 24 hours, until the temperature has been normal for 3 days. This usually requires a total of 5 to 6 days of drug therapy. Further investigations which are now in progress may alter this dosage recommendation.

Age.	Single dose (gr.).	Tablets.		Interval (hrs.).	Total 24-hr. dose (gr.).
		0.25 gm.	0.50 gm.		
Below 6 mos.	1.93	$\frac{1}{2}$	$\frac{1}{4}$	4	11.58
6 mos.-1 yr.	3.86	1	$\frac{1}{2}$	4	23.16
1-3 yrs. (incl.)	5.79	$1\frac{1}{2}$	$\frac{3}{4}$	4	34.74
4-6 yrs. (incl.)	7.72	2	1	4	46.32
7-9 yrs. (incl.)	11.58	3	$1\frac{1}{2}$	4	69.48
10-12 yrs. (incl.)	15.44	4	2	4	92.64

Summary. Seventy-seven of the infants and children admitted to the Pediatric Service of the Minneapolis General Hospital from January to July, 1940, with a diagnosis of pneumonia were given sulfathiazole—the thiazole analogue of sulfapyridine.

An attempt was made to type all of the cases by the Neufeld method. In many of the patients this procedure gave positive results revealing a fairly good distribution of the pneumococcus types. The remainder of the children who gave a negative or unsatisfactory Neufeld test did, however, have a lobar type of pneumonia.

Various doses of the sulfathiazole were tried and in doing this all ages of the children were fairly well represented.

The response to the sulfathiazole therapy was most encouraging. The patients took the drug well. There was little of the nausea and vomiting frequently encountered with sulfapyridine.

Toxic manifestations were few in number. The most disturbing feature of the chemotherapy was the appearance of a drop in the polymorphonuclear blood cells. With a discontinuance of the drug, the white blood cells soon returned to the normal figure.

Careful clinical observations of the patients receiving the various amounts of the sulfathiazole together with the determinations of the level of the drug in the free state in the blood permitted a dosage schedule to be established. It is presented with the understanding that although this will be of value to the practising physician at the present time, future clinical studies may produce changes which will give even better results.

THE DISTRIBUTION OF SULFANILAMIDE BETWEEN BLOOD AND CEREBROSPINAL FLUID WITH SPECIAL REFERENCE TO INTRASPINAL TREATMENT.

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SULFANILAMIDE compounds have been the subject of numerous comprehensive pharmacologic and pharmacodynamic studies. The special aspect of the passage of sulfanilamide from the general circulation into the cerebrospinal fluid has, however, received only

scant attention. Yet, such study deserves serious consideration for what it may contribute to our present knowledge of both the mode of action of the drug and its rational mode of administration in certain pathologic conditions.

The use of sulfanilamide in diseases of the cerebrospinal nervous system brings forward once more the much debated problem of whether or not it is necessary for a drug present in the general circulation to pass into the cerebrospinal fluid in order to affect the cerebrospinal nervous system. If it were satisfactorily proven that sulfanilamide passes from the blood into the cerebrospinal fluid (C.S.F.) rapidly and in relatively high concentrations there would be no indication for intraspinal administration of the drug. This would be recognized even by those investigators who feel that substances introduced into the blood reach the cerebrospinal nerve tissues *via* the C.S.F.⁶

Both clinical and laboratory studies have dealt with the subject here considered. Sulfanilamide has been recovered in the C.S.F. in man 4 to 5 hours after administration of the drug by mouth.⁷ In cases of meningitis in men marked differences were found between prontosil B (base) and prontosil S (soluble), with regard to their passage from the general circulation into the C.S.F. In a case of severe purulent meningitis it took 2 days before the daily dose of 1.8 gm. of prontosil B was found in the C.S.F. In the same patient prontosil S was detected the next day. On the other hand, in a case of mild meningitis neither prontosil B nor prontosil S could be detected in the C.S.F. after the oral administration of the former and the intramuscular administration of the latter. In another case of mild meningitis prontosil B given orally was not found in the C.S.F., whereas prontosil S given intramuscularly passed into the C.S.F.⁴ The content of sulfanilamide in the C.S.F. was found to vary considerably (1.2 to 17.8 mg. per 100 cc.) in 6 patients and not to bear any relation to the course of the disease or to the rapidity of sterilization of the fluid. Yet, experience suggests to the authors that the intraspinal way may prove to be a very efficient way of giving the drug.³ Sulfanilamide concentration proved to be similar in blood and C.S.F. "the first hours" after the administration of the drug. But during the "early hours" in the phase of ascent of the sulfanilamide content in blood and C.S.F. it was higher in the former than in the latter. The reverse was observed to 1½ to 2½ days after the onset of medication.¹ Because of differences in procedure, this study does not lend itself well for an analysis of the blood-C.S.F. sulfanilamide relationship. Malaria treatment has proven to favor the passage of prontosil from blood into C.S.F. Thus, in patients who received the treatment, prontosil permeated into the C.S.F., the amount being directly correlated with the globulin content of the C.S.F. On the other hand, in

patients without malaria treatment, prontosil was not found in the C.S.F.⁸ In patients with "intact" blood-C.S.F. barrier, examinations of blood and C.S.F. at hourly intervals and for 5 hours after the oral or parenteral administration of various sulfanilamides revealed the following results: Soluble prontosil given orally could not be detected in the C.S.F. Sodium sulfanilate in solution entered only in very small amounts; prontosil album showed the highest permeation. The latter was practically nil for dimethyl-disulfanilamide.⁹

Experimental studies showed that 30 minutes after the intravenous injection of prontosil S (2 cc. of 2.5% solution per kilo body weight) to normal rabbits only slight traces of the drug were found in the C.S.F. On the other hand, in 9 rabbits with artificially provoked acute or chronic meningitis—under otherwise similar experimental conditions—the concentration of the drug in the C.S.F. ranged between 0.374 and 1.140 mg. per 100 cc.⁵

Our own studies were carried out in 31 patients of this hospital. One common feature in all of them is the normal findings—protein, cells, and serologic reactions—in the cerebrospinal fluid. Otherwise, the patients may be divided into two groups: *A*, Patients with diagnosis of schizophrenia in whom both general physical and special neurologic examinations did not reveal any abnormal findings. *B*, Patients who in addition to their psychotic disorders are afflicted with varied organic diseases.

For the determination of sulfanilamide in blood and C.S.F. the method of Bratton and Marshall was used.²

A. Psychotic Patients With No Physical Disease. The 16 schizophrenic patients, from 26 to 42 years of age, were subdivided into two groups.

Group 1 (9 Patients): Each patient received by mouth therapeutic doses of sulfanilamide, namely, 25 grains every 6 hours—plus sodium bicarbonate 15 grains—a total of 100 grains in 24 hours. The medication was discontinued at the end of the third day.

Sulfanilamide* was analyzed in specimens of blood and C.S.F. obtained at the same time. Twenty-four hours after the beginning of the treatment, each of the patients having received 100 grains of sulfanilamide, the blood content of the latter varied from 4.26 to 8 mg. per 100 cc.; the spinal fluid content from 3.92 to 6.67 mg. per 100 cc.; and the permeability quotient $\left(\frac{\text{blood sulfanilamide}}{\text{C.S.F. sulfanilamide}}\right)$ from 1.1 to 1.68. At the end of 3 days' treatment, with a total of 300 grains, blood sulfanilamide values ranged from 6.25 to 8.6 mg. per 100 cc.; spinal fluid values from 5.06 to 7.6 mg. per 100 cc., and permeability quotient from 1.1 to 1.36. Twenty-four hours following the discontinuation of sulfanilamide its content varied in blood from 1.76 to 3.43 mg. per 100 cc., and in spinal fluid from 1.29 to

* Free sulfanilamide.

3.2 mg. per 100 cc., and the permeability quotients were between 1.35 and 1.88.

Group 2 (7 Patients): These patients also received 100 grains of sulfanilamide per day, in 4 equal doses, during 3 consecutive days; sodium bicarbonate was given with each dose of sulfanilamide. The difference in procedure, as compared to Group 1, consisted in extension of the analyses of sulfanilamide to 48 hours after cessation of the medication. Twenty-four hours after beginning of the treatment sulfanilamide ranged in blood from 4.7 to 8.0 mg. per 100 cc., and in spinal fluid from 3.35 to 5.92 mg. per 100 cc.; the permeability quotient varied from 1.06 to 1.59. The second day of the treatment, the blood level fluctuated from 6.15 to 10.88 mg. per 100 cc., the C.S.F. level from 4.52 to 8.25 mg. per 100 cc., and the permeability quotient from 1.17 to 1.44. On the third day of medication, the concentration in blood was between 6.06 and 12.31 mg. per 100 cc., and in C.S.F. between 4.5 and 10.13 mg. per 100 cc.; the permeability quotients were between 1.19 and 1.34.

Twenty-four hours after treatment was discontinued, blood sulfanilamide ranged from 2.0 to 5.8 mg. per 100 cc.; cerebrospinal fluid sulfanilamide from 1.5 to 4.94 mg. per 100 cc., and the permeability quotients from 1.12 to 1.5. Forty-eight hours after discontinuation of medication, sulfanilamide ranged from 0.66 to 3.0 mg. per 100 cc., in blood and from a trace to 2.73 mg. per 100 cc. in C.S.F., the permeability quotient in those cases in which the C.S.F. contained measurable amounts of sulfanilamide ranged from 1.09 to 1.2.

B. Psychotic Patients With Physical Diseases. Again, differences in procedure lead us to subdivide the 15 patients into three groups (3, 4, 5).

Group 3 (5 Patients Above 50 Years of Age): In addition to the psychiatric diagnosis of schizophrenia, the physical diagnoses were arteriosclerosis in 4 cases and cerebral lues in 1 case. These patients were also given 100 grains of sulfanilamide per day in divided doses. The essential difference in procedure lies in a more marked prolongation of medication in 4 cases, and in extension of analyses of sulfanilamide after cessation of medication in all 5 cases. The main interest in these 5 patients is centered, however, not so much on the sulfanilamide values during medication but rather on the behavior of the drug after cessation of the medication:

Thus, in 1 case (A1.) in which sulfanilamide was given for 3 days but analyses of the drug were followed for 5 days after its discontinuation the results were as follows: On the 1st day, sulfanilamide concentration dropped from 13.4 to 6.72 mg. per 100 cc. in blood, and from 9.75 to 6.61 mg. per 100 cc. in C.S.F.; the permeability quotient changed from 1.38 to 1.01. On the 2d day the blood content was 3.64 and the C.S.F. content 3.92 mg. per 100 cc.; the permeability quotient went down to 0.92. On the 3d day no sulfanilamide could be found in the blood, but 0.45 mg. per 100 cc. was still

present in the C.S.F. Tests on the 4th and 5th days, following cessation of medication, showed no traces of the drug in either blood or C.S.F.

Four patients were given sulfanilamide for 5 days, each receiving a total of 500 grains. Inasmuch as sulfanilamide in both blood and C.S.F. followed a similar trend in all the 4 cases, the findings in 1 case (Cr.) only are recorded: Two days after discontinuing treatment, sulfanilamide had fallen in blood from 14.54 to 3.48 mg. per 100 cc., and in C.S.F. from 12.3 to 5.92 mg. per 100 cc.; the permeability quotient changed from 1.18 to 0.58. Three days after cessation of medication sulfanilamide was 2.82 in blood and 3.48 mg. per 100 cc. in C.S.F.; the permeability quotient was still 0.81. Four days after completion of treatment, sulfanilamide in blood was 2.08 and in spinal fluid 1.92 mg. per 100 cc.; the permeability quotient rose to 1.08.

Thus, the cases of this group show that after medication with sulfanilamide at the rate of 100 grains per day for 5 days considerable quantities of the drug persist in the blood and spinal fluid as long as 4 days after discontinuation of the treatment.

Group 4 (5 Psychotic Patients With General Arteriosclerosis). In these patients the behavior of sulfanilamide in blood and C.S.F. was followed after a single dose (2 gm.) was given. Four hours after its administration, sulfanilamide in blood varied from 0.12 to 0.41, and in C.S.F. from 0.9 to 0.23 mg. per 100 cc.; the permeability quotient showed a wide variation, from 1.33 to 2.92. Twenty-eight hours later, sulfanilamide ranged in blood from 0.1 to 0.14 and in C.S.F. from 0.14 to 0.18 mg. per 100 cc.; the permeability quotient varied from 0.71 to 0.87.

Group 5 (5 Psychotic Patients With Organic Diseases). Paget's disease, 2 cases; arteriosclerosis, 2 cases; epilepsy-chorea, 1 case. As in Group 4, the patients received a single, but higher dose—5 gm.—of sulfanilamide. Four hours after the drug was given, its content in blood ranged from 3.41 to 7.7 and in C.S.F. from 1.68 to 4.13 mg. per 100 cc.; the permeability quotient varied from 1.87 to 2.33. Twenty-eight hours after administration of the drug, its concentration in blood was between 1.23 and 3.22 and in C.S.F. between 1.29 and 2.51 mg. per 100 cc.; the permeability quotients ranged from 0.84 to 1.23.

Comment. The outstanding feature in all our results is the passage of sulfanilamide from blood into C.S.F. in considerable concentrations, as compared to those in blood. This is readily seen in the permeability quotients $\left(\frac{\text{blood sulfanilamide}}{\text{C.S.F. sulfanilamide}} \right)$: Thus, in the 16 schizophrenic patients without organic disorders (Groups 1 and 2), the permeability quotients vary from 1.06 to 1.68 at the end of the 1st day of medication, from 1.17 to 1.44 at the end of the 2d day, and from 1.19 to 1.36 at the end of the 3d day of treatment.

In the 10 patients (Group 4 and 5) who received single doses (2 or 5 gm.) of sulfanilamide, the permeability quotients range between 1.33 and 2.92 four hours after administration of the drug, and between 0.71 and 1.23 twenty-eight hours after the drug was given. This considerable lowering of the permeability quotients suggests that after cessation of medication, blood loses sulfanilamide at a higher rate than the C.S.F. does. This suggestion becomes well-nigh a certainty when one considers the sulfanilamide values obtained within several days after cessation of treatment of 3 to 5 days' duration. Thus, the findings in the 2 illustrating cases (Al. and Cr.) of Group 3 demonstrate a gradual decrease of their permeability quotients during the 3 days following cessation of medication. These 2 cases also exemplify individual variations, all other conditions being similar. Thus, in Case Al. no sulfanilamide could be detected in either blood or C.S.F. 4 days after discontinuation of medication. In Case Cr. the permeability quotient rose the 4th day, and at the same time considerable concentrations of sulfanilamide were found in both blood and C.S.F. The relatively higher loss of sulfanilamide in blood than in C.S.F. admits the working, at least, of three mechanisms; namely, more rapid elimination of the drug from blood, its higher permeation from blood into C.S.F., slower penetration of the drug from C.S.F. into blood.⁶ This is not the occasion to discuss the relative effectiveness of each of the respective mechanisms. For our purpose it suffices to register and reëmphasize the fact that sulfanilamide not only readily penetrates from the general circulation into the C.S.F. but that it also is being eliminated more slowly from the latter than from the former.

Conclusion. Oral administration of sulfanilamide assures the penetration of the drug into the C.S.F. in concentration sufficiently high to render unnecessary intraspinal administration of the drug. It should be noted that in our cases there were neither clinical nor laboratory findings (the C.S.F. was normal) which would suggest meningeal involvement of any moment. Yet, it is principally in meningitides that sulfanilamide has heretofore found its therapeutic usefulness, and it is also in meningitis that the passage of the drug from the blood into C.S.F. is likely to be at a higher rate than in our cases, inasmuch as in inflammatory processes of the meninges (of infectious and aseptic origin) the permeability of the barrier between blood and C.S.F. is usually increased.⁶

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FAILURE OF PARA-AMINOBENZOIC ACID TO INHIBIT SULFONAMIDE RASHES AND FEVERS.

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A NUMBER of substances have the property of inhibiting the bactericidal action of the sulfonamide drugs on various types of bacteria. Materials which exhibit this property have been isolated from bacterial cells^{2,3,7} and from animal tissues.⁵ These substances have not yet been chemically defined. Peptones⁴ and coenzymes,⁹ under certain conditions, have also been shown to inhibit the bactericidal activity of sulfonamide drugs. Woods¹⁰ identified various fractions of yeast concerned in this action, and from an analysis of the chemical properties of the active fractions found that *p*-aminobenzoic acid exhibited a marked degree of inhibitory effect on the bactericidal action of sulfanilamide. Selbie⁶ demonstrated that mice infected with hemolytic streptococci could not be saved with sulfanilamide if *p*-aminobenzoic acid were administered at the same time.

In a separate communication, we have presented data which confirm and extend some of Woods' observations.⁸ Our results may be summarized briefly:

1. *In vitro*, there is a roughly linear relationship between the concentrations of sulfonamides that are bacteriostatic for pneumococci and the minimum amounts of *p*-aminobenzoic acid that inhibit that action. The inhibitory effect of *p*-aminobenzoic acid varies with the different sulfonamide compounds. For example, 0.004 mg. per 100 cc. of *p*-aminobenzoic acid inhibited the bacteriostatic effect on pneumococci of 10 mg. per 100 cc. of sulfanilamide; while 0.04 mg. per 100 cc. of *p*-aminobenzoic acid was required to overcome the action of 10 mg. per 100 cc. of sulfathiazole.

2. The action of sulfapyridine on pneumococci can be nullified at any stage short of complete killing by the addition of *p*-aminobenzoic acid. Pneumococci "revived" by this means grow like a similar number of viable organisms freshly inoculated into the same medium without sulfapyridine.

3. Para-aminobenzoic acid is readily absorbed after oral administration and is rapidly excreted in the urine. It is distributed in red

blood cells and blood plasma, though in higher concentration in the latter. The substance was administered to many subjects without untoward effects.

4. The pneumococcal action of human blood resulting from the administration of sulfapyridine and sulfathiazole can be overcome by the oral administration of *p*-aminobenzoic acid, even though sulfonamide therapy is continued.

5. Para-aminobenzoic acid excreted in urine or added to urine *in vitro* nullifies the bactericidal action of sulfathiazole on colon bacilli.

Results of (1) and (2) have been utilized clinically in the culture of body fluids from patients receiving sulfonamide therapy.

The suggestion has been made that *p*-aminobenzoic acid might inhibit not only the bactericidal action of the sulfonamide drugs, but also their toxic effects in human tissues.¹ To test this hypothesis the studies reported here were carried out. A type of toxic reaction to the sulfonamide drugs was sought which, 1, is an objective manifestation, 2, disappears quickly on withdrawal of the offending drug and, 3, reappears if the drug is again administered. Drug fevers and rashes were selected for study because they fulfill these criteria.

An attempt was first made to overcome drug fever by the administration of *p*-aminobenzoic acid. The following cases are illustrative:

Case Reports. CASE 1.—S. L., a 17-year-old colored female, was admitted to the hospital on July 15, 1940, with gonorrheal arthritis. Beginning on the day of admission, 1 gm. of sulfathiazole was given every 4 hours for the next 3 weeks. On August 7, the patient's temperature was slightly elevated and she complained of nausea and headache. The drug was then discontinued and for the next 10 days she was afebrile. On August 15, at 9 P.M., sulfathiazole treatment was begun again and continued with a dose of 1 gm. every 4 hours for the next 28 hours. Immediately after the first dose of sulfathiazole the patient complained of nausea and headache. Within 8 hours of the first dose the rectal temperature had risen to 101° F., and thereafter remained between 100° and 102° F. until sulfathiazole was discontinued. Seventeen hours after the first dose of sulfathiazole the patient was given 2 gm. of *p*-aminobenzoic acid. This dose was repeated at 3-hour intervals for the next 12 hours. Blood taken just before the first dose of *p*-aminobenzoic acid showed moderate pneumococcal power, while a blood sample taken after the second dose of *p*-aminobenzoic acid showed almost complete loss of this killing power. During the 12-hour period of *p*-aminobenzoic acid administration there was no amelioration of the patient's symptoms, nor was the temperature reduced. Twelve hours after the last dose of sulfathiazole the temperature was normal and the symptoms gone.

CASE 2.—L. C., a 50-year-old white male, was admitted with dysuria and fever. A diagnosis of cystitis and prostatism was made. Beginning on August 21, 1940, 1 gm. of sulfathiazole was given every 4 hours. The patient's temperature returned to normal in 3 days and his urinary symptoms disappeared. The drug therapy was continued. On August 30, the patient's temperature was elevated to 102.6° F. He was drowsy, sweating and nauseated. No rash was noted. There were no urinary symptoms.

Sulfathiazole was continued on the same dosage schedule and, in addition, 1 gm. of *p*-aminobenzoic acid was given at 2-hour intervals for the next 8 hours. During this time the temperature rose steadily to a maximum of 104.6° F., 8 hours after the first dose of *p*-aminobenzoic acid. At this time both drugs were discontinued. The temperature reached normal 12 hours later. Blood taken before the administration of *p*-aminobenzoic acid showed marked pneumococcidal action; blood taken after *p*-aminobenzoic acid had been given showed complete loss of killing power.

In these 2 cases, therefore, once sulfonamide fever had become manifest it could not be overcome or inhibited by the administration of *p*-aminobenzoic acid. The failure to overcome the drug fever was manifest in spite of the fact that the antibacterial property of the blood attributable to the sulfonamide therapy had been overcome by the *p*-aminobenzoic acid.

Additional patients were then selected who had previously exhibited signs of toxic reactions to sulfonamides. These patients were given *p*-aminobenzoic acid during and before a second course of sulfonamide therapy in an attempt to prevent a recurrence of drug toxicity. The results in 2 such cases may be described briefly:

CASE 3.—M. T., a 31-year-old white female, was admitted to the hospital with signs of pneumonia. Sulfathiazole was begun on the second hospital day and continued for the next 7 days. The temperature fell to normal on the sixth day. On the eighth day the temperature was again elevated and on the following day rose to 103° F. At the same time a diffuse erythematous morbilliform rash appeared. The drug was discontinued, and in 20 hours the temperature fell to normal and the rash faded completely. On the tenth day, 1 gm. of *p*-aminobenzoic acid was given at 2-hour intervals. With the third dose of *p*-aminobenzoic acid a single dose of 1 gm. of sulfathiazole was given. Two hours later the rash recurred and the temperature rose, both the rash and the fever reaching their height 9 hours after administration of the single dose of sulfathiazole. Twelve hours later the temperature was normal and the rash had again disappeared. The course of events is illustrated in Figure 1.

CASE 4.—G. N., a 72-year-old white male, had been hospitalized for many weeks because of a cerebral vascular accident. He was given sulfathiazole in an attempt to clear up severe decubitus ulcers. On the sixth day of sulfathiazole therapy an "erythema nodosum" type of rash was noted. It consisted of irregularly rounded, purplish-red nodules on the extensor aspects of the knees and forearms and on the cheeks and forehead. The drug was continued for 3 days more, during which time the temperature rose to 102° F. and the rash became more extensive. Five days later, when the temperature was normal and the rash had disappeared, a single 0.5 gm. dose of sulfathiazole was given. There were no toxic reactions during the next 48 hours. Para-aminobenzoic acid was then administered at 2-hour intervals over the next 52 hours, a total dose of 29 gm. Three hours after the first dose of *p*-aminobenzoic acid, sulfathiazole was again started and 13 gm. were given in the next 48 hours. Forty hours after the first dose of sulfathiazole the rash recurred and the temperature rose to 101° F. With the omission of both drugs, rash and fever disappeared. As a control, the patient was given *p*-aminobenzoic acid, without sulfathiazole, for a total of 33 gm. over a 66-hour period. During this time there was no recurrence of rash or fever. The course of events is shown in Figure 2.

The toxic effects of sulfathiazole therapy manifested by fever and rash were neither prevented nor cured by oral administration of *p*-aminobenzoic acid.

Comment. Fildes¹ expressed the view that *p*-aminobenzoic acid may be an "essential metabolite" in animal cells. By virtue of their structural similarity with this substance, the sulfonamides are

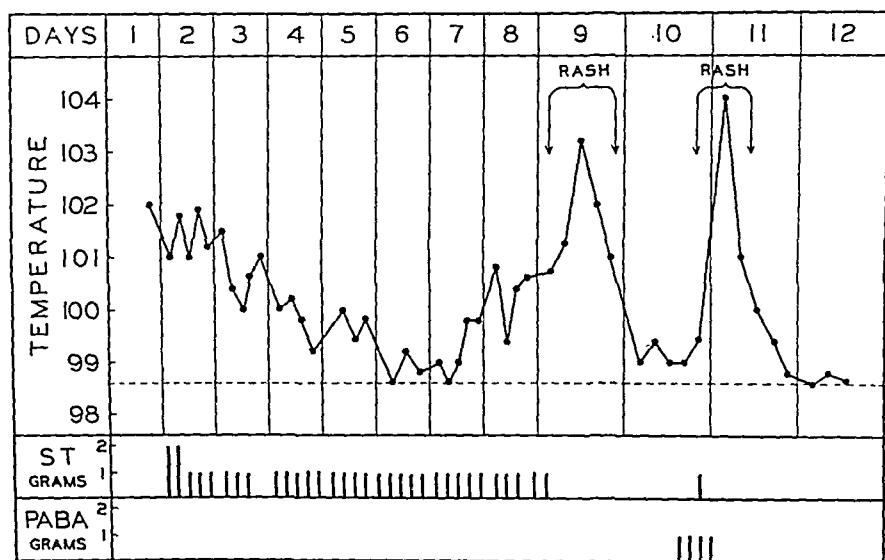


FIG. 1.—Failure to prevent recurrence of sulfathiazole (ST) rash and fever by administration of *p*-aminobenzoic acid (PABA) in Case 3.

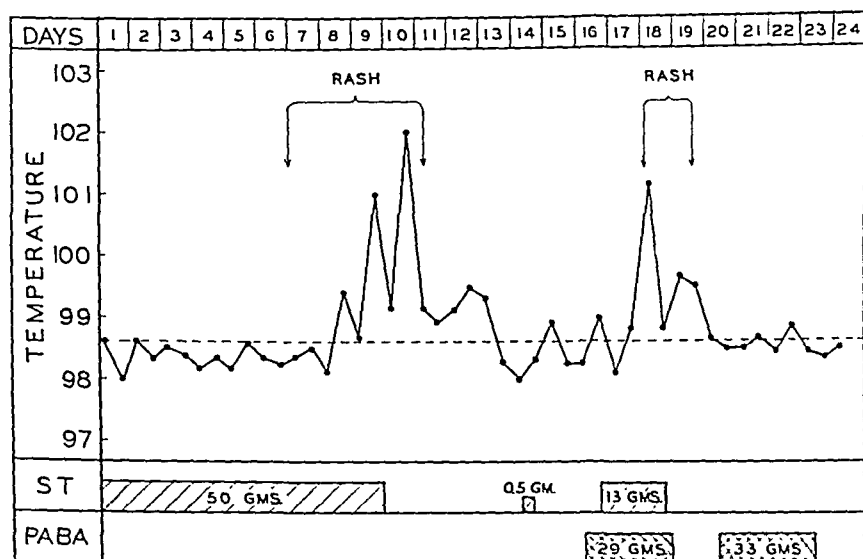


FIG. 2.—Case 4. Failure to prevent or to influence the recurrence of sulfathiazole (ST) fever and rash by administration of *p*-aminobenzoic acid (PABA) and the failure of the latter by itself to reproduce these symptoms.

thus considered to produce toxic effects in tissues by replacing *p*-aminobenzoic acid in the course of metabolic processes. Much of the data concerning the mode of action of the sulfonamides, including our studies previously summarized, are consistent with such an hypothesis in so far as it concerns bacterial growth. The present clinical observations, however, do not support this hypothesis with respect to toxic effects in human tissues.

The mechanism of the production of sulfonamide fevers and rashes is at present unknown. The various sulfonamide drugs differ not only in the frequency with which they produce these toxic reactions, but also in the variety of the cellular reactions. The possibility that *p*-aminobenzoic acid or other similar substances may prevent or overcome some other types of toxic reactions to sulfonamides has not been excluded. Investigations along these lines are still in progress.

Conclusions. Fevers and rashes due to sulfathiazole could neither be overcome nor prevented by the administration of *p*-aminobenzoic acid, even when given in amounts sufficient to overcome the antibacterial action of the sulfonamide drug in the blood and urine.

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THE MODE OF ACTION OF MAGNESIUM SULPHATE IN REDUCING THE HYPERTENSION OF ACUTE GLOMERULONEPHRITIS.*

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SINCE the introduction of magnesium sulphate, by Blackfan and his coworkers,^{3,4} for the lowering of the elevated blood pressure in the early phase of acute glomerular nephritis, extensive clinical experience with this substance has proven its efficacy. It is commonly held that cerebral edema is the primary stimulus bringing

* Aided by a grant for the study of Salt Metabolism from Mead Johnson & Company, Evansville, Ind.

about the hypertension of acute glomerulonephritis. The mechanism by which magnesium sulphate reduces this hypertension, however, has remained obscure. The generally advanced explanation for its *modus operandi* is that it is a dehydrating agent, promoting loss of water from the body with resultant cerebral dehydration.

The clinical experiments recorded here have been planned to elucidate the mode of action of magnesium sulphate in the patient with hypertension in acute glomerulonephritis, especially in relation to dehydration. The first series of observations were made to determine whether dehydration was associated with the fall in

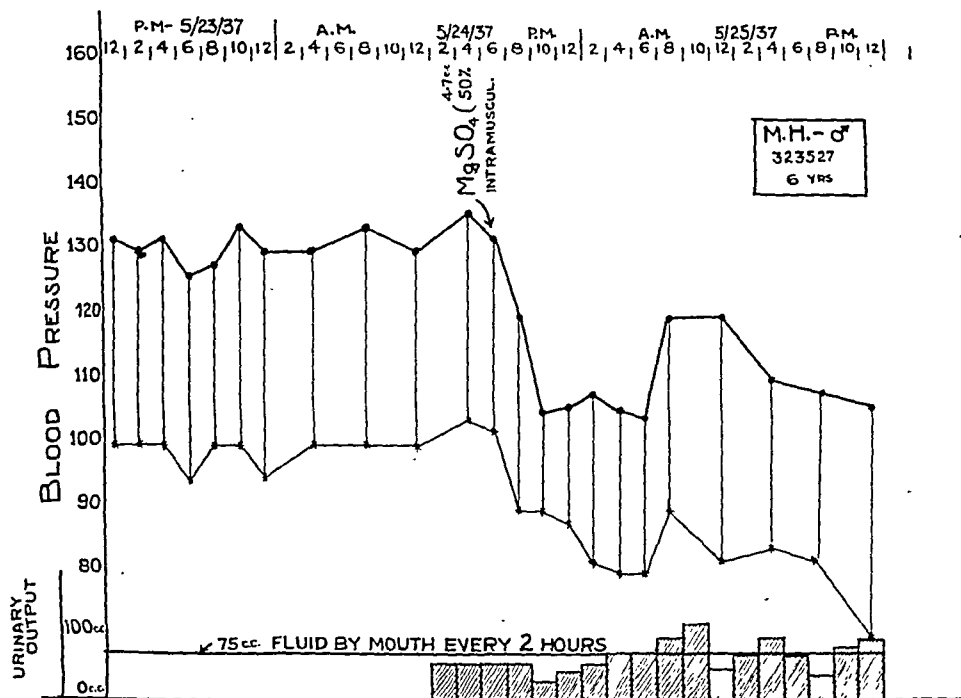


FIG. 1

blood pressure induced by magnesium sulphate given intramuscularly. Figures 1 and 2 are representative of such experiments. The patients were given fixed amounts of orange juice (75 cc.) at 2-hour intervals. Urine collections were made at these times. The blood pressure was taken at hourly periods. This régime was maintained for 12 to 24 hours before administration of magnesium sulphate, to ascertain the variability of the blood pressure. When the pressure had remained fairly stable for a period of about 6 hours, the magnesium sulphate (0.2 cc., 50% solution per kg. of body weight) was given into the muscles of the buttocks. It is apparent from the figures that there was no diuresis accompanying the fall in blood pressure. During the short period of the experiment, weight changes did not occur. It is, therefore, reasonable to conclude that

magnesium sulphate is able to lower the blood pressure without producing dehydration (loss of body water).

Approaching the problem from another viewpoint, the effect of a known dehydrating agent upon the hypertension was studied. If the original concept of magnesium action, viz., its dehydrating effect, were correct, then loss of water from the body produced by other means should be effectual in lowering the blood pressure. The intravenous administration of hypertonic sucrose (50%) was used for this purpose since it has been shown to produce dehydration, both general and cerebral.^{5,9} Patients were placed on a régime

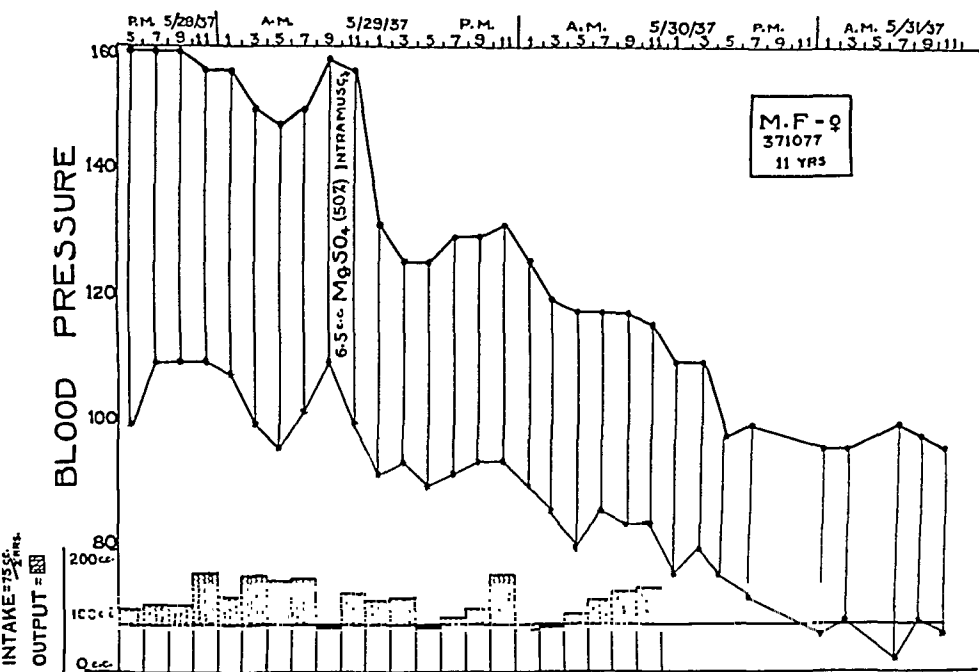


FIG. 2

FIGS. 1 and 2.—A lowering of the elevated blood pressure by the intramuscular injection of MgSO₄, without accompanying dehydration (*i. e.*, loss of water by diuresis).

similar to that in the magnesium experiment. Figure 3 depicts the result of one of these experiments. Following the injection of 100 cc. of 50% sucrose, free diuresis occurred. This was not followed by a fall in blood pressure.

Figure 4 represents the data obtained in a patient to whom both sucrose and magnesium were given in sequence. Following the injection of 50 cc. of hypertonic sucrose, there was diuresis with no fall in blood pressure. Fourteen hours after the sucrose administration, and while the blood pressure was still elevated, magnesium sulphate was injected. There followed a fairly rapid fall in blood pressure, with no associated diuresis. About 24 hours later, when

the blood pressure had again attained a higher level, twice the initial dose of sucrose was administered. The urinary output following this was even greater than that after the first sucrose injection, again with no effect on the blood pressure.

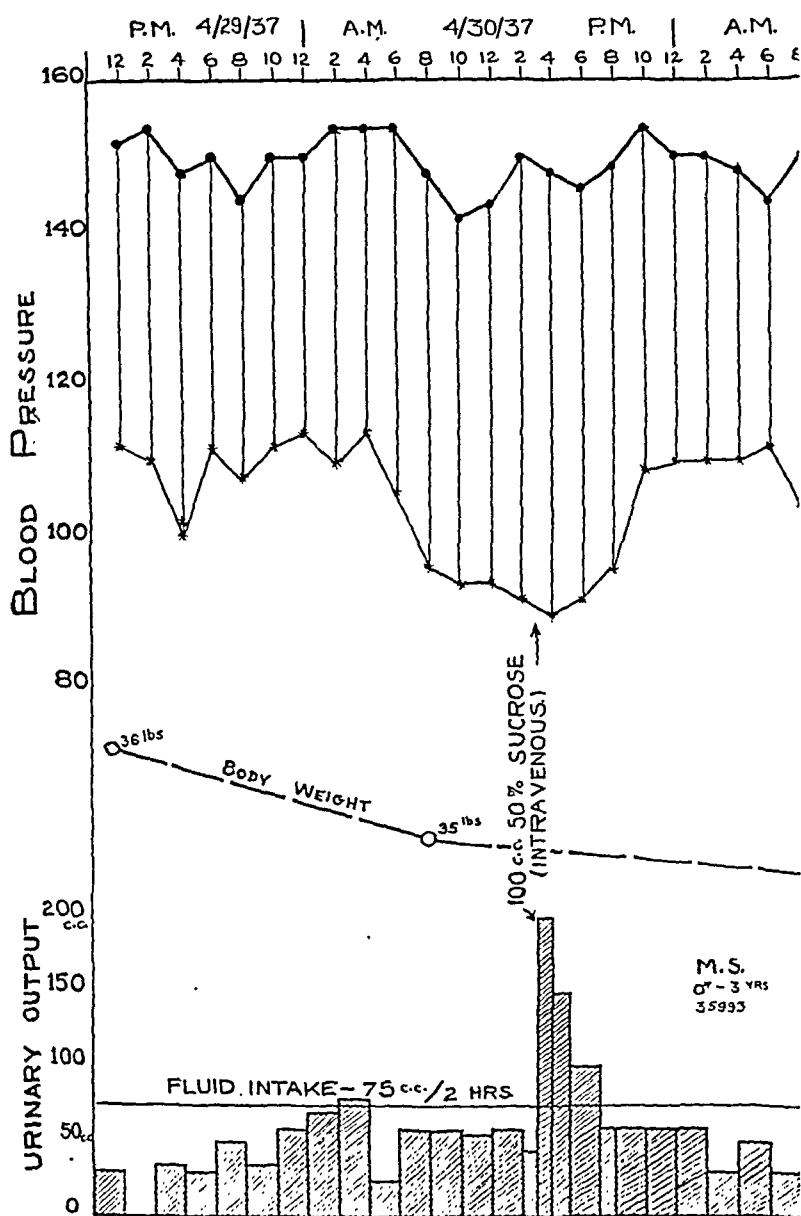


FIG. 3.—Failure of intravenous injection of hypertonic sucrose (50%) to lower the elevated blood pressure, while producing free diuresis.

Figure 5 is the chart of another patient with hypertension and hypertensive encephalopathy, whose period of observation began at 4 P.M., May 29, 1939. After the patient had been observed for

a period of 20 hours, during which time his urinary output, fluid intake, and blood pressure were carefully noted, he had a convulsion at 1 P.M., May 30, 1939, which was associated with a sharp rise in the diastolic blood pressure (this elevated diastolic reading was obtained while the patient was still convulsing). As the patient began to relax from the convulsion (the diastolic pressure had

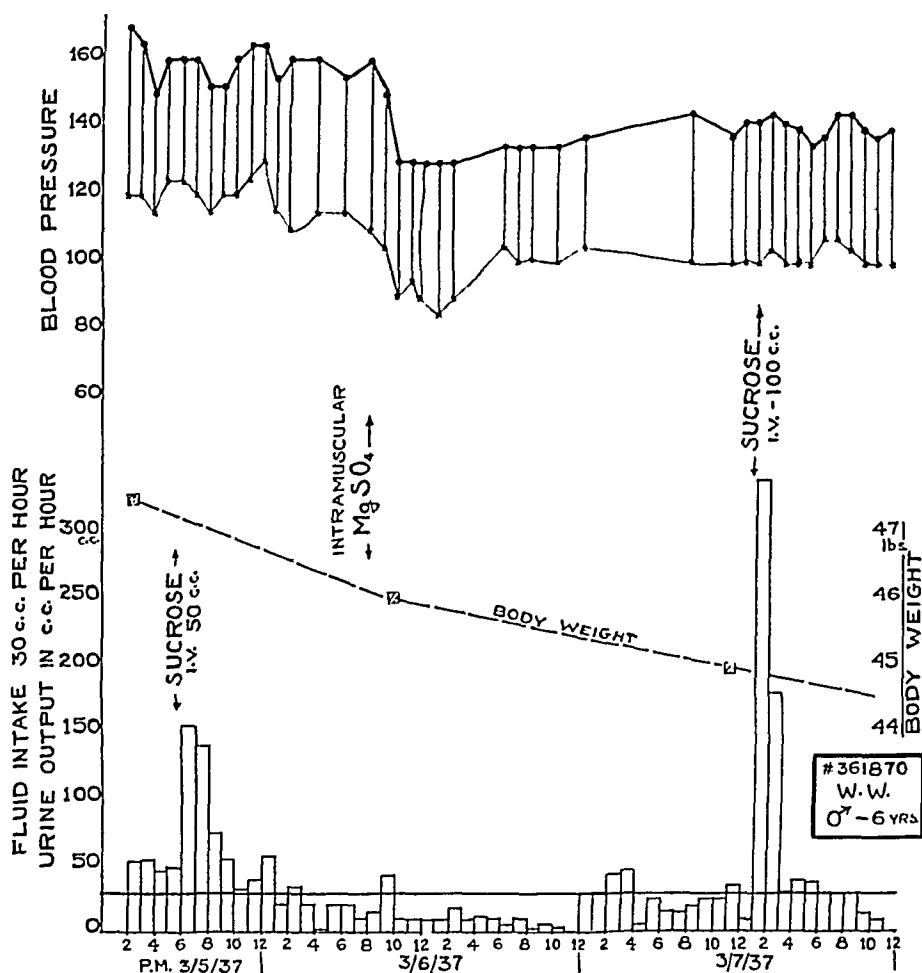


FIG. 4.—Free diuresis (dehydration) produced by the intravenously injected 50% sucrose—without any reduction of the blood pressure, followed by a reduction of the blood pressure produced by the intramuscular injection of $MgSO_4$ —without accompanying diuresis.

already begun to fall), 75 cc. of 50% sucrose were given intravenously. A marked increase in urinary volume followed, with no significant alteration in the blood pressure. At 5 P.M., 2 hours after the sucrose diuresis had subsided, the patient had another convulsion. Following this second convulsion, magnesium sulphate was injected and was followed by a rapid fall in the blood pressure,

both systolic and diastolic, without any increased urinary output. Concomitant with the fall in blood pressure, the patient became alert and interested in his surroundings. It is pertinent to note that the blood pressure both during and after the second convulsion was at the same high level recorded prior to the first convulsion, and only after the magnesium sulphate injection was there any significant depression of the hypertension. Occasionally, immediately

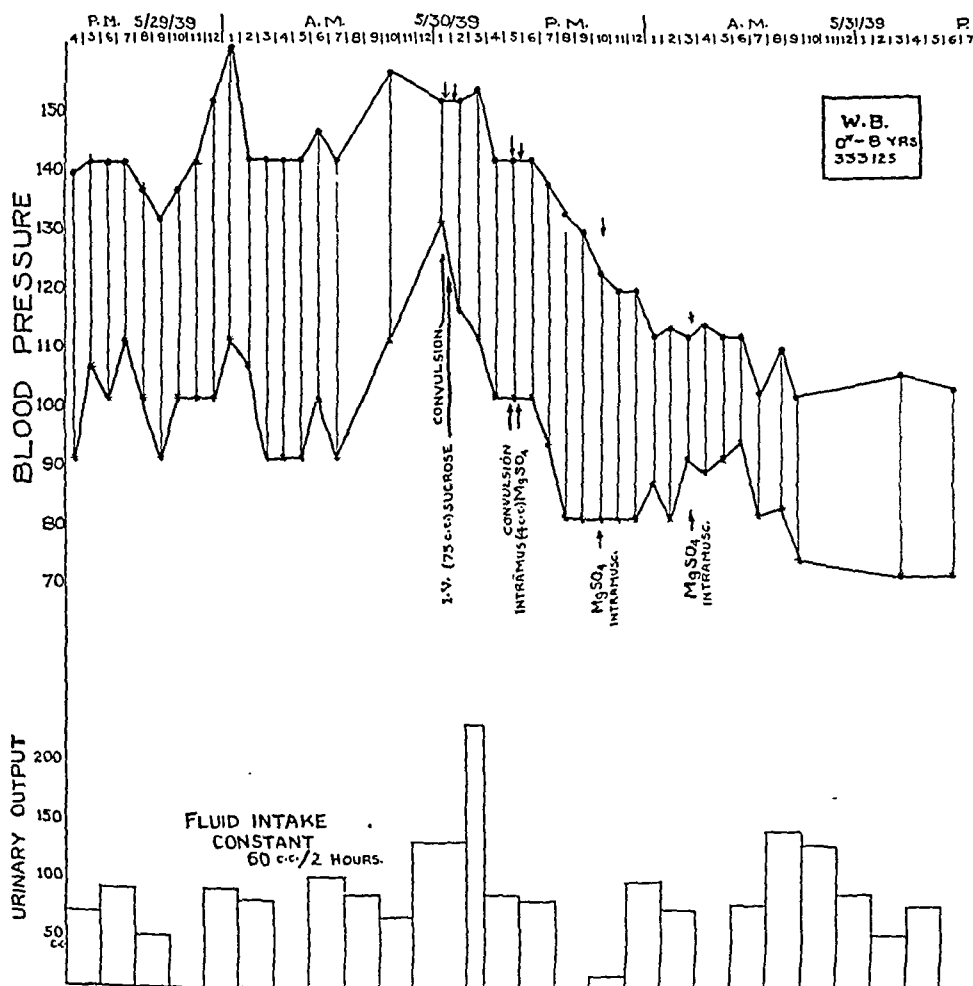


FIG. 5.—Reduction of the blood pressure by $MgSO_4$ after 50% sucrose given intravenously had produced a free diuresis but had failed to reduce the elevated blood pressure.

after sucrose is given, there is a transient elevation in the blood pressure (Fig. 6). This we have attributed to a temporary increase in blood volume induced by the hypertonicity of the sucrose solution, drawing fluid into the blood stream. Such an increase of blood volume has been found following sucrose administration.⁶ The giving of sucrose to acutely hypertensive glomerulonephritics

is not without danger for this reason. We have seen two instances where such patients were thrown into acute cardiac failure, presumably due to the sudden increase in blood volume.

The data thus far presented demonstrated that magnesium sulphate reduces the elevated blood pressure in these patients without producing diuresis. It is maintained, by those who hold that

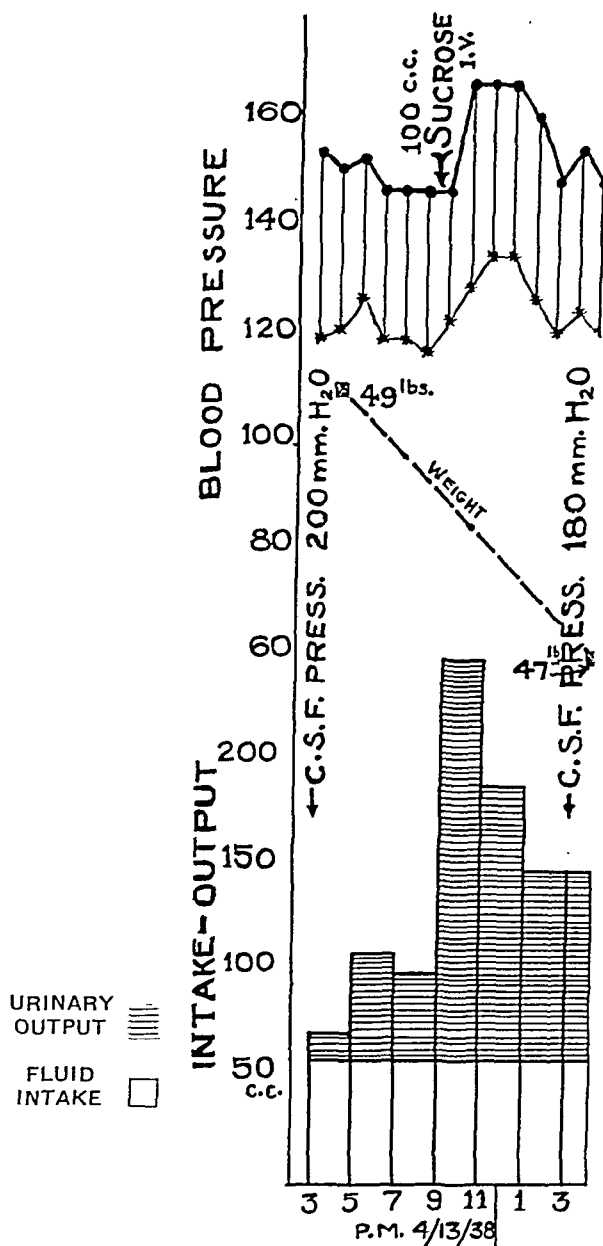


FIG. 6.—The relatively normal cerebrospinal fluid pressure in a child with hypertension and encephalopathy. Also the rise of the arterial blood pressure following the sucrose administration.

magnesium sulphate is operative through its dehydrating properties, that even though general dehydration might not occur with the small doses used, there does occur *localized cerebral dehydration*.¹ However, the inefficacy of hypertonic sucrose as a blood pressure reducing agent militates against this point of view. It has been amply demonstrated^{5,9} that 50% sucrose produces a marked fall in intracranial pressure, obviously through cerebral dehydration. Still with doses of hypertonic sucrose large enough to produce loss of appreciable quantities of body water, and by inference cerebral dehydration, no fall of the elevated blood pressure occurred. Thus, even if following the administration of magnesium sulphate, local cerebral dehydration were to occur (in the absence of general dehydration), it would seem unreasonable to conclude that the fall in blood pressure elicited by the magnesium sulphate did result from this cerebral dehydration. Similar observations were made on a group of patients with malignant hypertension and hypertensive encephalopathy by Murphy *et al.*,¹⁰ who report that following the injection of intravenous sucrose there was a marked fall in intracranial pressure, with no fall in the blood pressure. In fact, in accord with our observations, these investigators noted a slight rise in blood pressure after the sucrose injection.

Since magnesium sulphate apparently does not act by dehydration either generalized or local, in effecting reduction of the acute hypertension of patients with acute glomerulonephritis, what then is the mechanism of its action?

It has been demonstrated by Pickering¹¹ and others¹² that the hypertension of acute glomerulonephritis is dependent upon spasm of the smaller arteries producing increased peripheral resistance. It is known that magnesium can relax smooth muscle, including that of the vascular wall. In previous experiments,¹³ magnesium sulphate was effective in reducing the blood pressures of rats rendered hypertensive by large doses of ergotamine tartrate. Similarly, it produced relaxation of the smooth muscle of the guinea-pig uterus in Dale anaphylactic experiments. Hoff *et al.*⁷ in animal experiments showed that magnesium sulphate produced lowering of blood pressure by its vasodilating action. It is extremely dubious whether the depressing action that magnesium sulphate is known to produce on the heart is responsible for the fall in blood pressure noted in these studies, for the blood concentrations of magnesium necessary to produce cardiac change¹⁴ could not have been attained with doses of magnesium sulphate employed in this study. *Therefore, it might be concluded that magnesium sulphate lowers the blood pressure of the hypertensive child with acute glomerulonephritis by relaxing the existing generalized vasospasm through local action on the smooth muscle of the small blood-vessels.*

Blackfan² has inferred that this hypertension, which is dependent upon vasospasm, is induced in a large measure by cerebral edema,

since he observed increased cerebrospinal fluid pressure in his patients. However, he, too, seems uncertain as to whether the increased intracranial pressure is the primary event, since, according to him, none of the recorded pressures approach in any degree the magnitude of spinal fluid pressure necessary (800 mm. water) to produce the degree of hypertension noted in the glomerulonephritic. One of our cases (Fig. 6) showed the presence of hypertension in a child with very slightly elevated cerebrospinal fluid pressure.

Whether varying degrees of cerebral edema are present in all patients with acute glomerulonephritis having hypertension is not clear, nor is the mechanism of the occurrence of edema, when present, well understood. One possible explanation for this occurrence of edema may be some alteration in the cerebral circulation dependent upon vasospasm. Lewis and Gelfand⁸ have shown that in the capillaries distal to constricted arterioles there is increased permeability, as evidenced by exudation of fluid and diapedesis of red blood cells. However, that this phenomenon does occur in the brains of these patients has not been proven.

It is extremely difficult in the clinical consideration of hypertension in the child with acute nephritis to disregard some mention of the acute hypertensive encephalopathic episodes. The sequence of events during such attacks would appear to be: 1, a sudden rise in the blood pressure; 2, cerebral symptoms, such as stupor, headache, convulsions; 3, a fall in the blood pressure; and finally, 4, disappearance of the cerebral symptoms. As to the etiology underlying the cerebral attack, the general opinions may be divided into two groups, one being that cerebral edema is the cause and the other, that cerebral anemia (anoxemia) is the basis for the attack. That magnesium sulphate relieves the attack is well recognized, and that the disappearance of the attack is preceded by a fall in the blood pressure is also well known. We have demonstrated that magnesium sulphate reduces the elevated blood pressure without producing dehydration, and further in Figure 5 we present a case where the encephalopathic attack was not relieved by dehydration with sucrose. These observations seem at least to cast some doubt on the theory that cerebral edema is the basis for the encephalopathic episode.

The edema of the brain that has been shown to exist in these patients might be considered as an added factor in the symptom-complex, exaggerating the cerebral symptoms but not its primary cause. The induction of dehydration very likely relieves that part of the symptomatology dependent on the cerebral edema.

While the evidence presented seems opposed to the "cerebral edema" hypothesis, it does not follow that it sustains the "cerebral anoxemia" theory. Nevertheless, the rapid disappearance of the cerebral symptoms following vasorelaxation with magnesium sulphate does apparently lend some slight weight in the direction of this latter possibility.

There are many instances where the recommended dose of magnesium sulphate (0.2 cc., 50% magnesium sulphate per kilo body weight repeated every 4 hours) fails to lower the elevated blood pressure in these acute nephritic patients. In each such instance, with the possible exception of 1 of our patients, there was a fairly large urinary output (600 to 1000 cc. daily). Although we have no

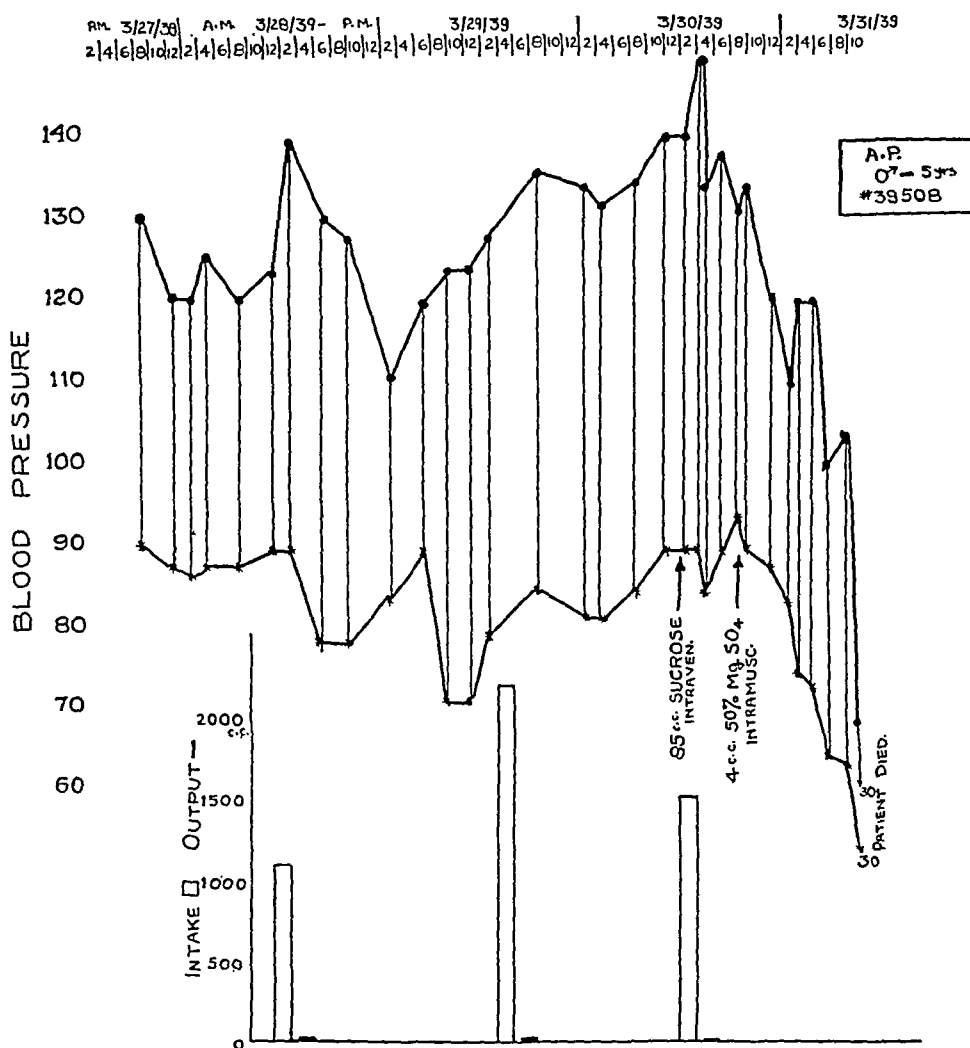


FIG. 7.—The exaggerated effect of $MgSO_4$ in lowering the blood pressure in an anuric patient.

data on the level of blood magnesium obtained in these patients, it seems probable that the failure in these instances of the magnesium sulphate to reduce the blood pressure may have been due to its rapid excretion from the body, with a failure to obtain a sufficiently high concentration of it in the body fluids for its physiologic action. Studies of Hoff, Smith and Winkler⁷ would seem to

substantiate this, for they found that a definitely elevated level of blood magnesium (3 to 5 m.Eq.) had to be attained to produce a fall in blood pressure. They further demonstrated that there was some correlation between the level of blood magnesium and the amount of fall in blood pressure. These data suggest that patients with large urinary outputs require larger doses of magnesium sulphate than employed by us to obtain a reduction in blood pressure. Figure 7 is the blood pressure and fluid intake—output record of a 5-year-old boy with acute glomerulonephritis, who had anuria. The record extends over his complete hospital stay, although there was a history of anuria for 2 days prior to his hospitalization. On the fourth day of his anuria, when the blood pressure was rising, he was given 85 cc. of 50% sucrose intravenously. This was followed by a rise in the blood pressure but no diuresis. Six hours later he was given one intramuscular injection of a therapeutic dose of magnesium sulphate. This was followed by a precipitate decline in the blood pressure, during which the patient expired. (While magnesium sulphate may have adversely affected this patient, we feel that his death was primarily due to uremia.)

This case is presented because it is felt that it summarizes several of the points which we have already advanced. First, it shows conclusively, that magnesium sulphate is effective as a blood pressure reducing agent without producing dehydration. It is analogous to the experiments performed by Hoff *et al.*⁷ where urinary excretion in their animals was suppressed by ligation of the ureters, prior to the administration of magnesium sulphate, so that the magnesium sulphate could be maintained at desired high levels in the body fluids. Thus the injection of one dose of magnesium sulphate into this anuric patient produced a maximal effect on the blood pressure. It further illustrates a possible danger of administering magnesium sulphate to an anuric patient.

Summary. In the patient with acute glomerulonephritis and hypertension: 1. Magnesium sulphate lowers the blood pressure without producing dehydration.

2. The intravenous administration of hypertonic sucrose produces diuresis, and generalized and cerebral dehydration, without lowering the blood pressure. Occasionally it elevates the blood pressure. The dangers of this secondary rise in blood pressure in the acute nephritic are pointed out.

3. Magnesium sulphate in the doses employed may be ineffectual in patients with large urinary volumes.

4. The mechanism by which magnesium sulphate reduces elevated blood pressure is discussed.

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ALIMENTARY AZOTEMIA: A CLINICAL SYNDROME OCCURRING AS A PART OF THE BLEEDING PEPTIC ULCER COMPLEX.

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THE occurrence of increased blood urea values in cases of bleeding peptic ulcer was first observed by Sanguinetti⁶ in 1934. Since that time the observation has been repeated by several writers and numerous theories have arisen as to the causation of the syndrome. Of the many theories, the three chief ones were dehydration and starvation (Meyler,⁵ 1933; Alsted,¹ 1936); shock (Crohn,³ 1939) and absorption of digested blood (Sanguinetti,⁶ 1934; Christiansen,² 1935; Schiff, Stevens, *et al.*,⁹ 1939; and Kaump and Parsons,^{4a,b} 1940). Other writers likened the condition to so-called "hepatorenal syndrome."

The importance of the syndrome of increased blood urea in these cases has been repeatedly emphasized. Its value in prognosis has been shown by Schiff⁸ in a report of 53 cases of hematemesis or melena in 1939. In a recent communication Schiff⁷ reported 133 cases of hematemesis and melena. The blood urea nitrogen exceeded 30 mg. per 100 cc. in 78 of the cases and was 50 mg. per 100 cc. or more in 26 of the 78 cases. Of the patients with a blood urea nitrogen of 30 mg. per 100 cc. or more, 16.9% died; 34.6% of those with an elevation of 50 mg. per 100 cc. or more died and 63.6% of those with an elevation of 70 mg. per 100 cc. or more died. In the 57 patients with a blood urea nitrogen of less than 30 mg. per 100 cc. there were no deaths, excluding 2 cases of ruptured aortic aneurysm.

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In the treatment of bleeding peptic ulcer the condition is also of importance. In a case where one is in doubt as to whether or not to operate, an increased blood urea due to renal or hepatic involvement might influence the decision far more than an elevation due to absorption of digested blood. It was because of this manifest difference in the importance of the syndrome depending on its cause that we started the present studies.

CAUSATION OF THE INCREASED BLOOD UREA VALUES. In 13 experiments, on healthy dogs, whole beef blood was administered by stomach tube in large single and divided doses. A maximum blood urea nitrogen concentration was attained in all cases in from $5\frac{1}{2}$ to 19 hours, depending on the amounts of blood given and the number of doses. The return of blood urea nitrogen to normal levels occurred in from 6 to $17\frac{1}{2}$ hours following the last administration of blood as shown in Chart I.

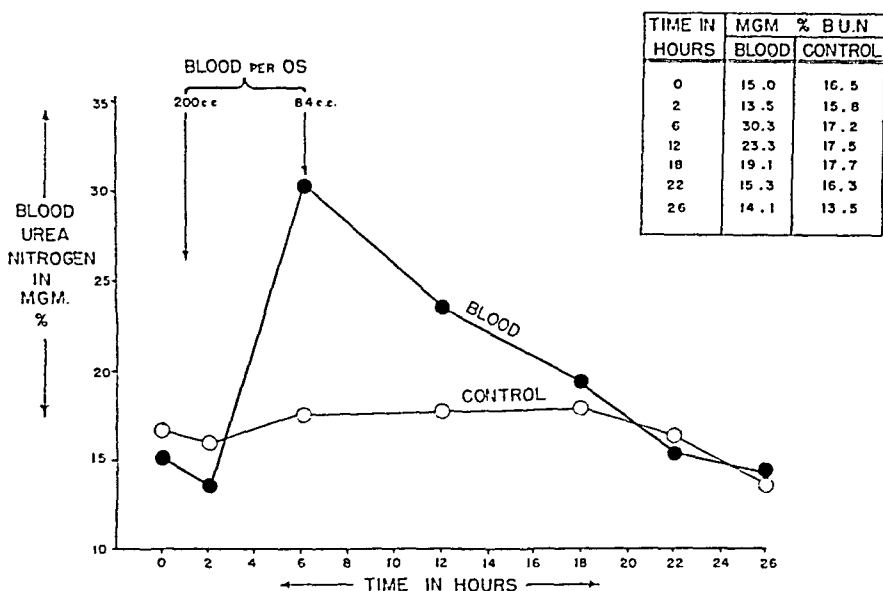


CHART I.—The effect of blood in the production of alimentary azotemia. The solid circles represent the blood urea nitrogen curve of the dog given blood by stomach tube while the hollow circles represent the curve of the control animal.

In a second series of ten experiments, 5 dogs were given beef blood cells by stomach tube in divided doses, and 5 dogs were given beef plasma in divided doses.

The 5 dogs given blood cells showed an elevation of blood urea nitrogen above normal within 4 hours and a maximum concentration at intervals between 5 and 12 hours. The return to normal levels required from 12 to 17 hours following the last dose of blood cells.

The 5 dogs given beef plasma by stomach tube showed a longer interval between first administration of plasma and the initial rise of

blood urea nitrogen, occurring from 4 to 11 hours. The maximum concentration was apparent at intervals of from 8 to 11 hours, 1 dog showed no elevation above normal. The return of the blood urea nitrogen to normal following the last dose of plasma required from $5\frac{1}{2}$ to 20 hours. It is evident from Chart II that the blood urea nitrogen values were higher for the animals that received blood cells than for the animals that received plasma. This difference occurred even when the doses of plasma were double that of cells.

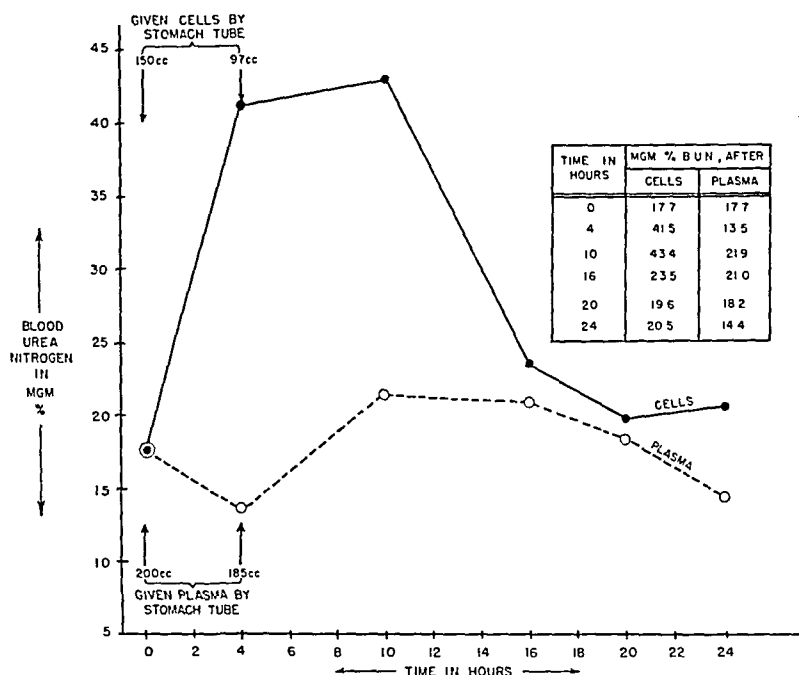


CHART II.—The comparative effects of blood cells and blood plasma in the production of alimentary azotemia. The solid line represents the blood urea nitrogen curve of the dog given red blood cells by stomach tube while the broken line represents the curve on the animal given blood plasma in the same manner.

To carry this aspect of the investigation further, another experiment was done using 2 dogs. One dog was given 60 gm. of pure hemoglobin in two 30-gm. doses 4 hours apart. The second dog received 100 gm. of pure hemoglobin in one 60-gm. and one 40-gm. dose 4 hours apart. As is seen in Chart III, both dogs showed an initial increase in blood urea nitrogen in 4 hours, a maximum concentration in 12 hours, and a return to normal in 28 hours. However, the dog that received the larger dose of hemoglobin showed consistently higher blood urea nitrogen values.

Blood urea nitrogen concentration determinations were made on 2 cross-circulated dogs in terminal traumatic shock of 3 hours' duration. These values were 21.9 mg. per 100 cc. and 22.9 mg. per 100 cc. respectively. These were only slightly elevated above normal, and represent what is in many cases only the upper limit of

normal. Autopsy of both dogs revealed gross hemorrhagic congestion of the mucosa of the entire small bowel.

Chart I, of the blood urea nitrogen curve following administration of whole blood in the dog, agrees with Schiff *et al.*⁹ similar experiments on humans.

"ALIMENTARY AZOTEMIA": A PROPOSED NEW TERM. The name azotemia has been applied to this syndrome ever since Sanguinetti⁶ wrote his first description of it. The word azotemia means the presence of urea or other nitrogenous bodies in the blood especially in increased amounts.

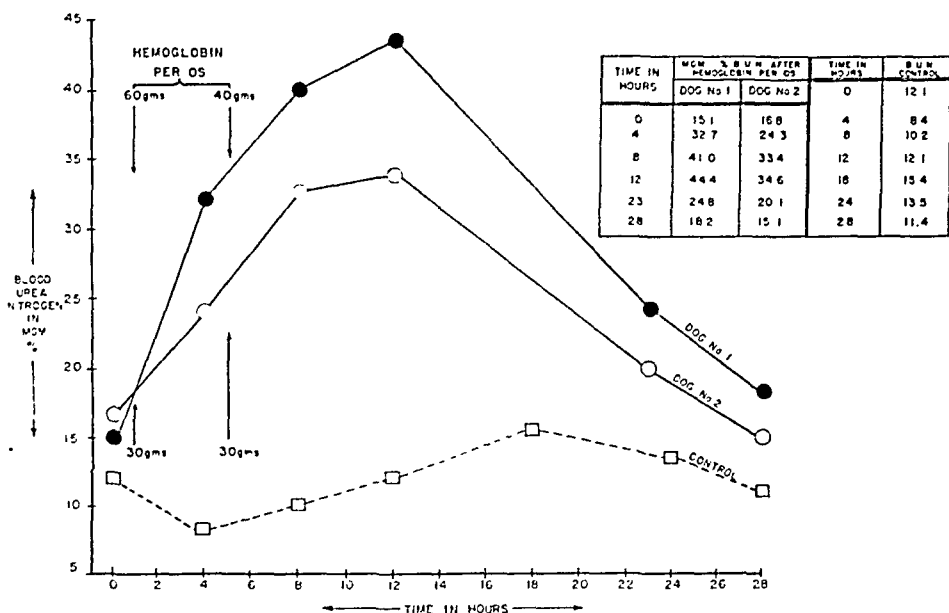


CHART III.—The effect of hemoglobin in the production of alimentary azotemia. The two solid lines represent the blood urea nitrogen curves of dogs given hemoglobin by stomach tube and the broken line represents the curve of the control animal.

Reasoning from analogy to the commonly used term "alimentary glycosuria" (which might be more properly termed "alimentary hyperglycemia") it seemed logical to us that the urea syndrome be termed "alimentary azotemia." The mechanism in each case is the same and the adjective is used in both instances to differentiate the condition under consideration from a similar one in result but a different one in causation. Use of the designation "extrarenal azotemia" is not definitive enough and furthermore leads to confusion with the so-called hepatorenal syndrome which we believe is not at all related to the condition we are considering.

Conclusions. Alimentary azotemia occurs in cases of massive hemorrhage into the intestinal tract. This in turn most often results from a bleeding peptic ulcer. The degree of the azotemia is of considerable prognostic significance, high blood urea nitrogen

values being associated with high mortality. This is probably because the increase in blood urea nitrogen is a measure of the amount of blood lost. Our experiments indicate that the increase is due to absorption of digested blood, and therefore for this condition the name "alimentary azotemia" is proposed. Finally, we have shown that the increase is mainly due to the erythrocyte fraction of blood (and in particular to its contained hemoglobin), while the plasma fraction plays a distinctly secondary rôle.

Alimentary azotemia, therefore, can be defined as an azotemia due to absorption of digested hemoglobin from the alimentary tract, the condition occurring clinically most often in patients with bleeding peptic ulcer.

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VITAMIN C STUDIES IN THE AGED.

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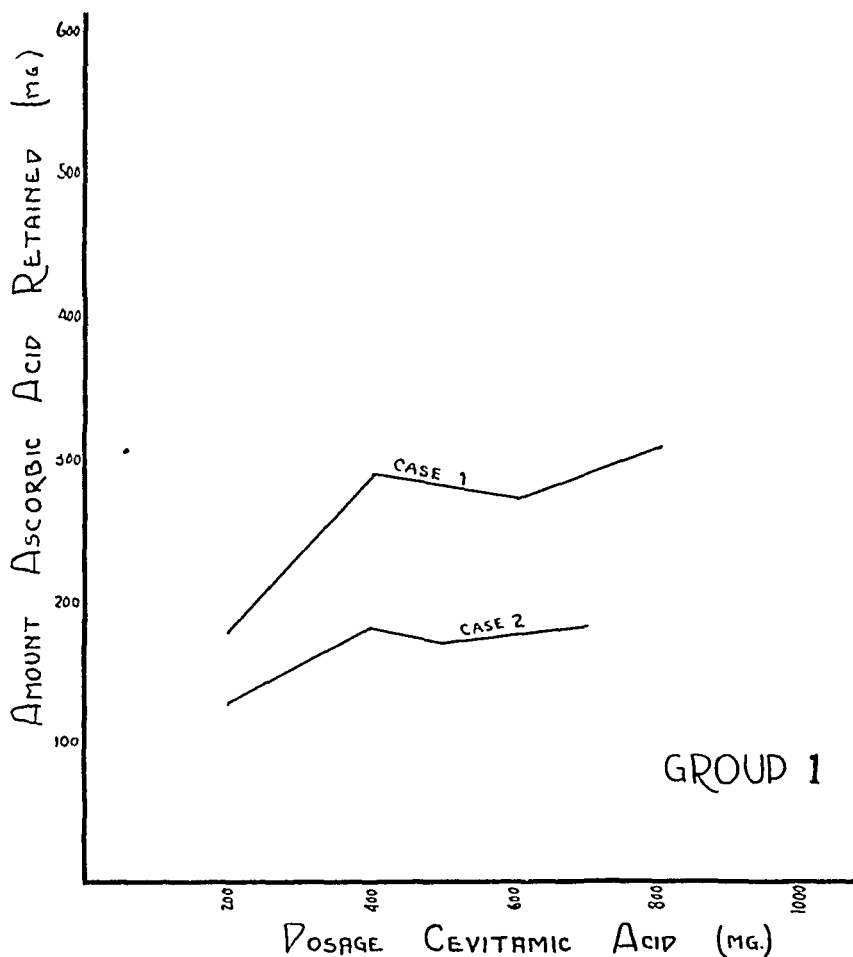
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(From the Hospital and Home of the Daughters of Jacob.)

VITAMIN C studies have been carried on extensively in infants and children and numerous articles have been written on the clinical significance of vitamin C deficiency in adults. Scant attention, however, has been paid to vitamin C studies in the aged. The only reports thus far have been those of Gander and Niederberger¹ and Kirchmann.³ Gander and Niederberger administered cevitic acid to a series of 14 patients (average age, 73 years) in daily doses of 200 mg. for a period of 4 days, followed by daily doses of 400 mg. In most of their cases urinary excretion of cevitic acid did not increase until a total of 2000 mg. had been received. Kirchmann determined the cevitic acid levels in a series of 50 patients, ranging in age from 50 to 87 years. Only 1 patient who had been living on an exclusively vegetarian diet for years was found to have the so-called normal cevitic acid level of 1 mg. per 100 cc. No American investigators, to the best of our knowledge, have reported on vitamin C studies in the aged. It was therefore thought of interest to investigate vitamin C retention and excretion in aged individuals.

This study is based on a series of 25 so-called "normal" aged men and women. Their ages ranged from 66 to 83 years; 14 were men and 11 were women. The subjects who were chosen for this study were individuals who were not suffering from any active disease, were housed in the "Home" division of the institution and were ambulatory. In 10 of the cases, oranges, tomatoes and lemons were part of their dietetic intake.



Method. The amount of cevitic acid* in the blood 1 hour after the noon-day meal and in the urine at the end of 24 hours was determined. These readings were regarded as our controls. Then, varying amounts of cevitic acid were administered by mouth, starting with a dosage of 100 mg. and increasing this by 100 to 200 mg. doses over a period of time. The cevitic acid was gradually increased until the saturation point was reached as evidenced by a sharp drop in the curves showing the amount of cevitic acid retained. This was computed by subtracting the number of milligrams excreted from the amount given, as plotted against the

* The cevitic acid, oral and injectable, was supplied through the courtesy of Hoffmann-La Roche, Inc., Nutley, N. J.

TABLE 1.

Case No.	Age.	Sex.	Date.	Dose of cevitamic acid (mg.).	Cevitamic acid in blood (mg. per 100 cc.).	Urinary excretion of cevitamic acid (mg. per diem).	Cevitamic acid retention (mg.).
1	76	♂	4- 5-40	Control	0.2	9	
			4-17-40	200	1.1	21	179
			4-26-40	400	2.4	110	290
			5- 5-40	600	2.8	327	273
			5-17-40	800	3.1	490	310
2	79	♂	4-11-40	Control	1.7	82	
			4-26-40	200	2.9	73	127
			5- 4-40	400	3.1	219	181
			5- 9-40	500	Not determined	329	171
			5-18-40	700	3.8	517	183
3	77	♀	7- 9-39	Control	0.4	10.8	
			7-15-39	100	0.4	18.8	81
			7-23-39	200	1.0	14.3	186
			8-27-39	400	0.92	97	303
			9-19-39	600	Not determined	143	257
			10-27-39	700	Not determined	340	360
4	77	♂	4-10-40	Control	0.8	38.8	
			4-16-40	200	1.4	59.8	140
			4-25-40	400	2.1	179	221
			5- 5-40	600	3.1	312	288
			5-12-40	800	3.8	490	310
5	72	♀	5- 1-40	Control	0.6	11.8	
			5- 8-40	200	1.3	29.9	170
			5-16-40	400	2.9	210	190
			5-24-40	500	3.2	380	120
			6- 2-40	700	3.6	430	270
6	72	♂	5- 5-40	Control	0.6	7	
			5-16-40	200	1.0	26	174
			5-24-40	400	2.1	89	311
			6- 1-40	600	0.9	133	467
			6-17-40	900	3.2	390	510
7	73	♀	5- 6-40	Control	0.3	7.2	
			5-12-40	200	0.6	19	181
			5-18-40	400	1.1	67	333
			5-26-40	600	1.8	104	496
			6- 2-40	800	3.6	214	586
8	69	♀	6-10-40	1000	3.8	397	603
			5- 6-40	Control	0.7	11	
			5-12-40	200	1.8	30	170
			5-18-40	400	2.4	103	297
			5-25-40	600	Not determined	194	406
9	73	♀	6- 2-40	800	Not determined	340	460
			8-27-39	Control	0.42	22	
			9-21-39	200	0.78	19	181
			10-18-39	400	1.2	77	323
			11- 4-39	500	Not determined	90	410
10	79	♂	11-29-39	600	1.9	122	478
			12-25-39	800	2.7	480	320
			1-14-40	1000	3.1	540	460
			3-29-40	Control	0.7	17.9	
			4- 6-40	200	Not determined	86.8	112
			4-17-40	300	1.9	129	171
			4-28-40	500	2.9	380	110
			5- 3-40	700	Not determined	410	290
			5-12-40	900	Not determined	650	250

TABLE 1—Continued.

Case No.	Age.	Sex.	Date.	Dose of cevitamic acid (mg.).	Cevitamic acid in blood (mg. per 100 cc.).	Urinary excretion of cevitamic acid (mg. per diem).	Cevitamic acid retention (mg.).
11	73	♂	7-17-39	Control	1.7	22.6	
			8-24-39	200	1.6	67	133
			9-14-39	400	1.4	107	293
			10- 7-39	500	1.6	129	371
			11-10-39	600	1.9	390	210
			11-27-39	700	2.4	520	180
12	73	♂	7-14-39	Control	0.4	23	
			9-21-39	200	1.0	11	189
			10- 7-39	400	Not determined	97	303
			11-10-39	500	2.3	390	110
13	66	♀	7- 5-39	Control	0.9	0	
			7-16-39	100	1.0	7	93
			7-23-39	200	1.2	13	167
			7-30-39	300	1.6	82	218
			8-22-39	400	1.4	17	383
			8-30-39	500	1.0	17	483
			9-14-39	600	1.1	38	562
			10-20-39	800	2.1	173	627
			11-27-39	1000	2.7	830	170
14	68	♀	1- 2-40	Control	0.38	11.3	
			1-27-40	200	1.7	29	171
			2-29-40	400	2.7	53	347
			3-16-40	500	2.8	99	401
			3-29-40	700	2.6	177	523
			4-10-40	900	3.7	410	490
15	66	♀	5- 1-40	Control	0.73	16	
			5- 9-40	200	1.3	39	161
			5-20-40	400	1.9	98	302
			6- 2-40	600	2.6	167	443
			6- 7-40	800	3.4	314	486
			6-12-40	1000	Not determined	611	389
16	73	♀	4-25-40	Control	0.57	12	
			5- 5-40	200	1.0	34	176
			5-18-40	400	1.4	81	329
			6- 2-40	600	Not determined	136	464
			6- 7-40	800	2.9	380	420
			6-16-40	1000	3.8	642	358
17	80	♂	7-14-39	Control	1.2	13	
			7-25-39	100	0.8	30	70
			9- 3-39	200	1.3	33.5	164
			9-30-39	400	1.8	58	342
			10-17-39	600	2.0	110	490
			11-24-39	800	2.3	290	510
			12- 7-39	900	2.6	580	320
18	81	♂	11-19-39	Control	0.5	10.1	
			12-19-39	200	1.9	29.7	170
			1- 7-40	300	2.8	40.2	260
			2-19-40	500	2.6	106	394
			3- 3-40	600	3.5	212	388
			3-11-40	800	3.9	479	321
19	71	♀	8-15-39	Control	0.92	4.1	
			9-19-39	200	0.9	41	159
			10-16-39	400	1.3	120	280
			11-29-39	500	1.5	122	378
			12- 5-39	700	2.6	350	350

TABLE 1—Continued.

Case No.	Age.	Sex.	Date.	Dose of cevitic acid (mg.).	Cevitic acid in blood (mg. per 100 cc.)	Urinary excretion of cevitic acid (mg. per diem).	Cevitic acid retention (mg.).
20	68	♂	4- 4-40	Control	0.74	32	
			4-10-40	200	1.4	32	168
			4-17-40	300	1.8	97	203
			4-21-40	500	2.8	126	374
			4-29-40	700	3.3	410	290
			5- 7-40	900	Not determined	698	202
21	68	♀	7-23-39	Control	1.6	76	
			8-24-39	100	1.4	84	16
			8-31-39	300	1.8	116	184
			9-14-39	500	3.1	219	281
			9-24-39	700	Not determined	419	281
			10-17-39	900	3.9	710	190
22	83	♂	8-17-39	Control	0.6	12.2	
			8-30-39	200	1.4	19.9	180
			9-11-39	400	2.0	37	363
			9-30-39	500	2.7	113	387
			10-31-39	600	1.9	260	340
			11-19-39	800	3.1	620	180
23	61	♂	4- 1-40	Control	0.39	14.8	
			4- 9-40	200	0.9	34	166
			4-18-40	400	1.4	126	274
			4-29-40	600	2.9	239	361
			5- 5-40	800	3.3	608	192
24	79	♂	7- 3-39	Control	0.7	13.6	
			7-16-39	100	1.5	22.3	78
			9-14-39	200	1.3	19.8	180
			9-29-39	400	Not determined	77	323
			10- 9-39	600	0.95	190	410
			10-30-39	800	2.2	610	190
25	81	♂	5- 3-40	Control	0.4	2	
			5- 9-40	200	2.4	19.7	180
			5-16-40	400	2.3	97	303
			6-24-40	600	3.3	219	381
			6- 2-40	800	3.8	288	512
			6-16-40	1000	3.6	496	504

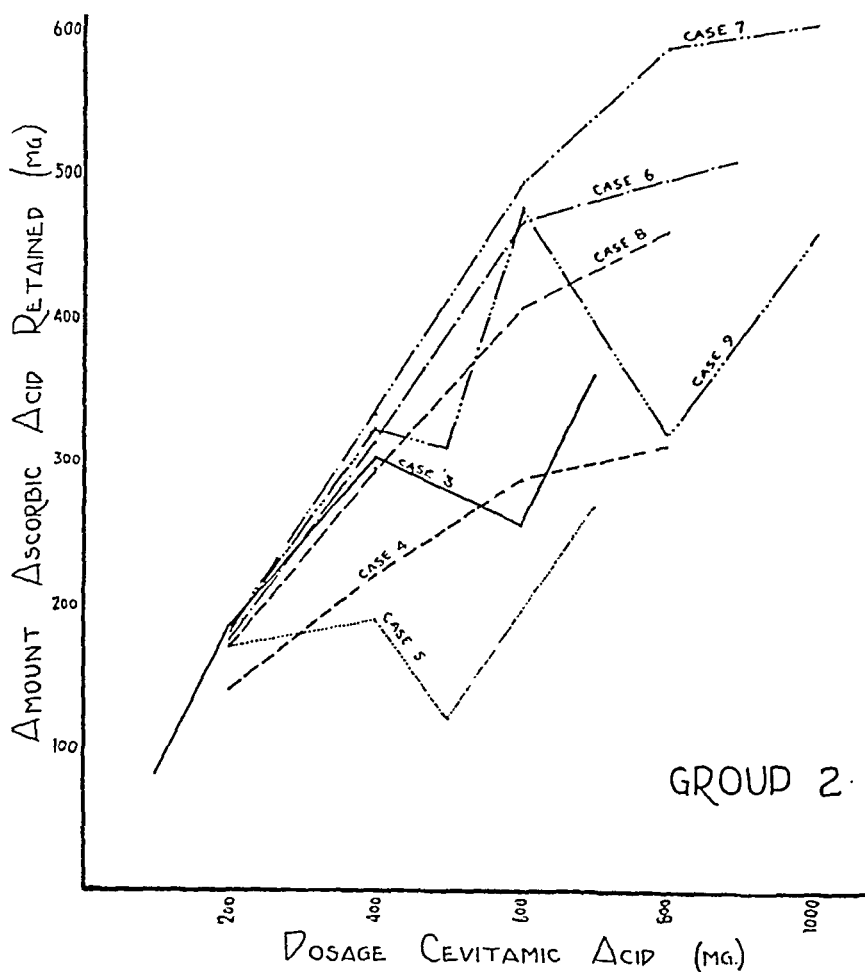
amount of cevitic acid administered. No more than 1000 mg. of cevitic acid were given as a single dose to any one subject because diarrhea was experienced by some with this dose. The periods chosen for the administration and determination of vitamin C were selected far enough apart to ensure the complete excretion of the previous dose.

The blood levels of cevitic acid were determined by Tillmans' method as described by Pijoan and Klemperer⁴ and the determination of cevitic acid in the urine was made by a modification of Tillmans' method as employed by Harris and Ray.²

Clinical Studies. The dosage of cevitic acid, the days on which it was given, the blood levels, the urinary excretion and the amount retained in the system are given in Table 1. In the accompanying graphs the number of milligrams of cevitic acid which was retained has been plotted against the number of milligrams of cevitic acid administered.

The levels of the retained cevitic acid seemed to indicate three types of curves:

1. A more or less constant level (Cases 1 and 2).
2. A constant upward trend during the period these experiments were carried out (Cases 3 to 9).
3. A rise until a peak was reached and from there on a downward trend (Cases 10 to 25).

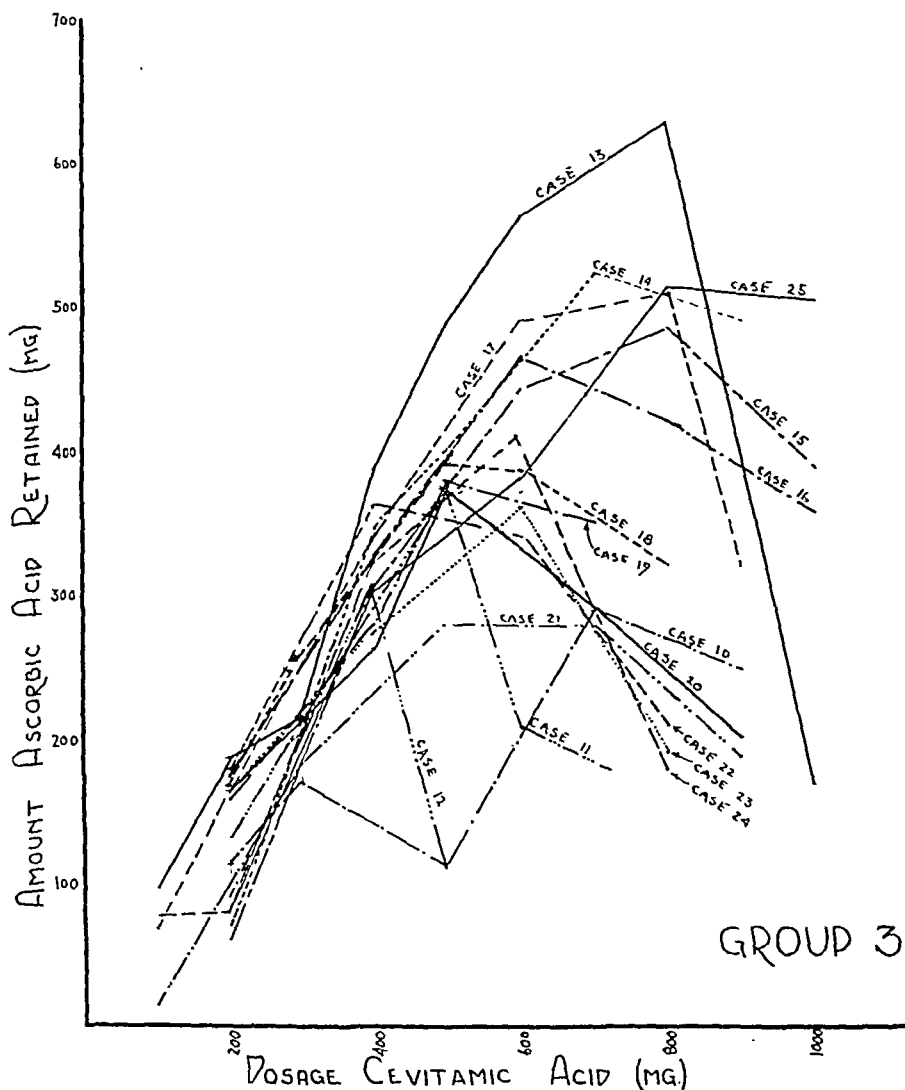


When the cevitic acid was given in large amounts, the blood levels of cevitic acid were likewise found to be appreciably high. The maximum levels were reached at the end of $\frac{1}{2}$ to 1 hour, whether administration was oral or intravenous. The highest level reached in the blood after 1000 mg. of cevitic acid given by mouth was 3.8 mg. at the end of 1 hour and when given intravenously the maximum level varied in 1 case from 4.5 mg. in 1 hour with a dose of 400 mg. to 4.2 mg. in $\frac{1}{2}$ hour in another case with a dose of 1000 mg.

Comment. When cevitic acid was given in comparatively large amounts to 25 so-called "normal" aged individuals, cevitic acid retention was noted in most of the subjects and the blood

levels of cevitic acid were likewise appreciably high. The cevitic acid retention curves were grouped as follows:

GROUP 1. In this group a more or less steady level of retained cevitic acid was noted. Irrespective of the amounts given, the excretion and retention closely followed the same pattern. These levels would seem to indicate that the saturation point was reached with relatively smaller doses as compared with most of the subjects under study.



GROUP 2. In this group, the cevitic acid retention continued to increase notwithstanding the fact that constantly larger doses were administered. No saturation point was observed during the time these experiments were carried out. It would be logical to assume from these curves that the subjects in this group required increasingly larger doses of cevitic acid.

GROUP 3. In this group comparatively large amounts of cevitic acid seemed to be required before the levels of cevitic acid retention showed a drop. It is difficult to explain just why there should be less retention with maximum doses of cevitic acid, unless a reserve of sufficient magnitude had been stored in the system from the previous doses that further cevitic acid was not required. In this group, the cevitic acid retention level, after reaching the peak, showed a variable drop from a slight to a sharp descent.

The maximum blood levels of cevitic acid did not show any appreciable changes which could be related to the avenue of administration, whether oral or intravenous. This was of special interest in view of the rôle which the factors of assimilation, absorption and utilization play in vitamin studies.

The relationship of cevitic acid retention to arteriosclerosis, which more or less accompanies old age, was of interest to us. This phase of the study is still under investigation and no definite conclusions have been found.

Conclusions. In a series of 25 so-called normal aged individuals, who received comparatively large doses of cevitic acid, only 2 showed a more or less constant saturation point. In the rest, high retention values were observed; in fact, in 7 cases the amount of retained cevitic acid continued to increase throughout the experiment.

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SCARLATINIFORM ERYTHEMA WITH SYSTEMIC REACTION FOLLOWING INUNCTION WITH MERCURIAL OINTMENT.

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DURING the past 4 years (1936 through 1939), 8 patients were referred to this hospital with a diagnosis of scarlet fever in whom we believe mercurial ointment inunctions were responsible for the scarlatiniform erythema. This error is understandable when one remembers that such patients often have fever and other evidences of systemic infection. All of the patients gave the same history, namely, repeated inunctions with blue ointment for the treatment of pediculosis. Detailed description of the cases will be presented after a preliminary historical review.

It has long been known that mercury, however taken into the body, is capable of producing mild to severe systemic reaction

including scarlatiniform erythema. Indeed, Bonetus⁶ in 1687 describes a case of "antipathy to mercury" in which the sensitive subject's hands and arms became red, itchy, and swollen merely on touching the metal. Other authors, Bell⁵ in 1793, and Spens¹³ in 1805, published reports concerning an erythema produced by mercurial inunction, but it was Alley² in 1810 who first gave an excellent description of the skin reaction and mentioned its close resemblance to the rash of scarlet fever. Alley classified the reactions as follows: *A*, hydrargyria mitis—without fever; *B*, hydrargyria simplex—with fever; *C*, hydrargyria maligna. He then described the above clinical types in some detail: "In *A*, there occurs an eruption of true miliary vesicles. The appearance of the vesicles is announced by a sense of heat and smarting on the surface of the skin. The only constitutional reaction is headache and nausea. The efflorescence, though not close at first, is gradually diffused over the whole surface of the parts affected so that they, and sometimes the entire body, present one uniform suffusion of tint. The color of the eruption recedes when pressure is applied and suddenly returns when pressure is removed. There may or may not be desquamation in this mild form. In *B*, the eruption is preceded by languor, restlessness and rigors, is accompanied by much itching and heat of the skin and the latter is considerably rough to the touch. There is also headache, whiteness of tongue and costiveness. The eruption may resemble rubella at this time. There is always greater or less fever (102°–106° F.) and the disease now also resembles measles. When on the decline, the eruption bears a great similarity to scarlatina anginosa. The cuticle separates here in larger areas than in the former, and desquamation is usually preceded by soreness of the throat. In *C*, there is a painful sense of burning on the skin surface. Soreness of the throat is prominent. The color of the eruption is darker, almost purple at times. Vesicles of large size are formed and there is edema of the subcutaneous tissue. Desquamation occurs in large flakes. The finger and toe nails may separate."

There have been many theories regarding the pathologic physiology of mercurial erythema. One of the most promising was proffered in 1888 by Lesser¹⁰ who suggested that the mercury circulating in the blood stream caused paralysis of the sympathetic nerves with consequent capillary dilatation. That capillary dilatation is the primary effect of mercury on the skin is supported by the histologic studies of Almkvist⁴ in 1922. In these studies he found that there was first vascular dilatation and transudation of fluid from vessels to tissue spaces, then cellular infiltration, and finally, bacterial invasion. He noted that the maximum capillary dilatation occurred at the summits of the papillæ, a fact which accounts for the punctate appearance of mercurial rashes and their close resemblance to the punctate erythema of scarlet fever.

Later literature is replete with reports of scarlatiniform erythema due to mercury in various forms and administered by various routes. Outstanding among these are papers by Alexander,¹ Caspary,⁸ Allgeyer,³ Thibierge,¹⁴ Milian^{11a} and Wright.¹⁵

Case Reports. CASE 1.—(Hosp. No. 421.) S. K., a 22-year-old white male was admitted on Feb. 5, 1936, with a chief complaint of fever and rash of 2 days' duration. The patient had been applying an unspecified amount of blue ointment to the skin of the pubic region for 5 days prior to entry. On the fifth day of treatment he suddenly developed a temperature of 102.4° F. and felt chilly. On the sixth day there was a bright red generalized rash and on the seventh day of treatment he was referred to the hospital with a diagnosis of scarlet fever. Admission examination revealed a well-developed and well-nourished male who did not appear acutely ill. He complained of considerable itching of the skin. The temperature was 102.4°, the pulse 98, and the respirations 18. Examination of the skin revealed a bright erythema over the chest, abdomen, and extremities. The rash on the trunk was confluent and punctate in character, while on the extremities it was macular. The most intense erythema appeared in the pubic region, the site of application of the ointment. The face alone was clear.

Head: eyes, ears, nose negative. *Mouth:* teeth and gums normal. Tongue white. Palate normal. Pharynx: moderately red. Tonsils injected. *Neck:* no enlargement of lymph nodes. *Chest:* lungs clear; heart negative. *Abdomen:* negative. *Genitalia:* normal except for intense erythema over pubic region; no pediculi seen. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative.

Course in Hospital. On symptomatic treatment, the temperature fell to normal on the fourth day and remained so throughout the remainder of the hospital stay. On the fifth day the rash faded except for a small area over the pubic region. He was discharged from the hospital on the seventh day of his illness. There was no desquamation except at the pubic region.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 2.—(Hosp. No. 537.) S. B., a 20-year-old white male, was admitted on Feb. 12, 1936. The patient had applied blue ointment for the treatment of pediculosis for 7 days prior to the onset of the present illness. He had used the ointment over his entire body with the exception of his face. On the seventh day of treatment he had malaise with fever of 102°. On the eighth day, his throat felt sore, and on the tenth day he developed a rash and was referred to this hospital with a diagnosis of scarlet fever. On entry, examination was as follows: Temperature 101.6°, pulse 100, respirations 20. The patient appeared acutely ill, with a livid eruption of fine punctate, closely-set papules over the trunk and extremities. The erythema was sharply demarcated at the neck and at the wrists and ankles. The face was clear.

Head: eyes, ears, nose negative. *Mouth:* profuse salivation; teeth normal; gums boggy and red. Pharynx: injected; tonsils small, injected. *Neck:* cherry-sized lymph nodes palpable. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* skin of pubic region showed fine desquamation as well as intense erythema. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative to routine examination, but Reinsch test for mercury was positive. Blood count: hemoglobin 85%. Red cells 3,700,000. White

cells 6200; neutrophils 82%, lymphocytes 9%, monocytes 9%. Throat culture: negative for *beta*-hemolytic streptococci.

Course in Hospital. The patient was given 10% sodium thiosulphate intravenously for 3 days. The temperature remained elevated at 101° and the rash persisted. On the sixth day of illness the patient was transferred to another hospital. At this time there was fine desquamation over the trunk; this was most evident in the axillæ and in the pubic region.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever. Mercury poisoning.

CASE 3.—(Hosp. No. 5062.) M. F., a 20-year-old white male, was admitted on Nov. 2, 1936. The patient had been treating himself for pediculosis for 10 days prior to entry. He had applied an unspecified amount of blue ointment to the groins, axillæ, and sternal region. On the tenth day of treatment there was sudden onset of headache, sore throat, and fever. On the next day he noticed a rash, first at the sites of application of the ointment, but soon becoming generalized. He was referred to this hospital with a diagnosis of scarlet fever. Examination revealed an acutely ill patient, with temperature 102.2°, pulse 110, and respirations 20. There was generalized erythema, punctate in the groins, axillæ, and over the sternum, but macular elsewhere. The eruption was most marked over the upper back where the lesions were hemorrhagic. The face was clear.

Head: eyes, ears, nose negative. *Mouth:* teeth—fair condition; gums soft and spongy; tongue beefy red. *Pharynx:* moderately red; tonsils injected. *Neck:* no lymph node enlargement. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* pubic hair shaved; there is excoriation of scrotal skin with dry scaling. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative; Reinsch test for mercury negative. Blood count: hemoglobin 90%. Red cells 4,000,000. White cells, 5800; neutrophils 83%, lymphocytes 12%, monocytes 4%, eosinophils 1%. Throat culture: negative for *beta*-hemolytic streptococci; positive for Vincent's organisms.

Course in Hospital. On symptomatic treatment, the temperature came to normal on the fifth day of illness; the rash faded and was completely gone on the seventh day after onset. Desquamation was present in the axillæ, groins, and sternal region.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 4.—(Hosp. No. 4964.) G. M., a 23-year-old white male, was admitted on Oct. 23, 1937. The patient had been using blue ointment in both groins for pubic pediculi for 2 days prior to onset at which time he noticed a bright, generalized erythematous rash. There were no other symptoms, but on the appearance of the rash he was referred to this hospital with a diagnosis of scarlet fever. On entry, the temperature was 98.8°, the pulse 80 and the respirations 20. He was not acutely ill. The skin presented a bright erythema, confluent over the trunk and blotchy over the extremities. The rash was purpuric in character over one small area on the anterior chest.

Head: eyes, ears, nose negative. *Mouth:* gums and teeth normal; tongue white. *Pharynx:* markedly reddened; tonsils large and red. *Neck:* small anterior cervical nodes palpable. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* normal. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative. Blood count: hemoglobin 80%. Red cells 5,040,000. White cells 6750; neutrophils 76%, lymphocytes 20%, monocytes 2%, eosinophils 2%. Throat culture: *Staph. aureus*; negative for *beta*-hemolytic streptococci.

Course in Hospital. At no time did the patient have fever. Daily urine examination was negative. He was discharged from the hospital on the sixth day of illness with the rash faded but not entirely clear. There was fine desquamation in the groins.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 5.—(Hosp. No. 5021.) J. L., a 31-year-old white male, was admitted on Aug. 19, 1938. The patient had been applying blue ointment to the entire body intermittently for the past month prior to entry. He was taken ill rather suddenly with high fever and a brilliant erythematous rash and was referred to the hospital with a diagnosis of scarlet fever. On entry he was acutely ill with temperature of 105°, pulse 120, respirations 22. The skin presented a bright confluent erythema over the trunk, becoming blotchy over the extremities. The face was clear.

Head: eyes, ears, nose negative. *Mouth:* teeth carious; gums reddened; tongue beefy red. *Pharynx:* red; tonsils out. *Neck:* no lymph node enlargement. *Chest:* lungs clear; heart: tachycardia, no enlargement, no murmurs. *Abdomen:* negative. *Genitalia:* pediculi present in pubic region. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative; Reinsch test for mercury negative. Blood count: hemoglobin 75%. Red cells 4,000,000. White cells 4200; neutrophils 52%, lymphocytes 47%, monocytes 1%. Throat culture: negative for *beta*-hemolytic streptococci.

Course in Hospital. The patient was given symptomatic treatment during which time the temperature ranged between 101° and 104° for the first 4 days, coming to normal on the fifth day. The rash faded with the subsidence of the temperature. A fine desquamation was noted over the trunk. The patient was discharged from the hospital on the eighth day of illness.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 6.—(Hosp. No. 6025.) C. P., a 21-year-old white male, was admitted on Dec. 11, 1938. He had used four tubes of blue ointment for the treatment of pediculosis. The ointment had been applied to the axillæ and groins for 1 week when he developed fever, sore throat, and an erythematous rash. He was referred to this hospital with a diagnosis of scarlet fever. On entry his temperature was 103°, pulse 120 and respirations 20. The skin examination revealed a generalized blush, lobster-red in color. There were vesicles superimposed on an intense erythematous base in the groin.

Head: eyes, ears, nose negative. *Mouth:* teeth in fair condition; gums spongy; tongue white. *Pharynx:* moderately red; tonsils out. *Neck:* no lymph node enlargement. *Chest:* lungs clear; heart normal except for tachycardia. *Abdomen:* negative. *Genitalia:* scaling erythematous eruption present; pediculi present in pubic region. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative. Blood count: hemoglobin 80%. Red cells 4,000,000. White cells 6200; neutrophils 84%, lymphocytes 14%, monocytes 2%. Throat culture: positive for Vincent's organisms. No *beta*-hemolytic streptococci grown.

Course in Hospital. With symptomatic treatment the temperature gradually fell to normal on the eighth day of the illness, but the rash had not completely faded until the tenth day. Desquamation appeared in the groins. This desquamation was fine or "branny" in character.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 7.—(Hosp. No. 1621.) E. K., a 17-year-old white male, was admitted on April 17, 1939. For 3 days prior to entry he had applied blue ointment because of pediculi. On the second day of treatment, he complained of soreness in his throat. The next day he had fever and a bright red rash and was referred to this hospital with a diagnosis of scarlet fever. On entry he appeared moderately ill. The temperature was 101°, pulse 100 and respirations 20. He was salivating quite profusely. The skin of the trunk was erythematous, and this erythema was most marked in the axillæ and groins where it was also punctate in character.

Head: eyes, ears, nose negative. *Mouth:* gums white and swollen. *Pharynx:* moderately injected; tonsils small, not remarkable. *Neck:* no enlarged nodes. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* erythema with vesiculation in pubic region and groins. *Pediculi* present. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. *Urine:* trace of albumin present on admission; Reinsch test for mercury negative. *Throat culture:* *Strep. viridans*; no beta-hemolytic streptococci grown.

Course in Hospital. The patient's temperature remained elevated for 6 days, coming to normal on the seventh, at which time the erythema had also faded. There was some fine desquamation in the groins and axillæ; none elsewhere.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 8.—(Hosp. No. 2916.) J. H., an 18-year-old white male, was admitted on Aug. 10, 1939, with a 10-day history of intermittent applications of blue ointment to the skin of the axillæ and groins. On the tenth day of treatment he was suddenly seized with headache and fever of 102° to 103° F., followed in 24 hours by a generalized rash. His throat felt sore at the time of the appearance of the rash. He was brought to this hospital with a diagnosis of scarlet fever. Physical examination revealed a young adult who was quite ill, with a temperature of 102.2°, pulse 100, respirations 22. His skin presented a diffuse generalized erythema which was definitely purpuric in the axillæ and groins. In the latter areas there was also blistering.

Head: eyes, ears, nose normal. *Mouth:* gums normal; teeth in good condition; tongue white. *Pharynx:* injected; tonsils large, moderately injected. *Neck:* no enlarged nodes. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* purpuric erythema with blistering on both groins. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. *Urine* negative. *Throat culture:* *Staph. aureus*; negative for beta-hemolytic streptococci.

Course in Hospital. The temperature ranged from 101° to 103° for the first 4 days and then came to normal on the fifth day. The rash faded completely by the eighth day. There was considerable coarse desquamation in the axillæ and groins, but none elsewhere.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

Comment. On reviewing the various clinical aspects of the foregoing 8 cases, it is seen that the blue ointment had been applied in the majority of cases from 5 to 7 days before a systemic reaction occurred and that the skin reaction was accompanied by fever of 101° or over in all but 1 patient (Case 4). The average duration of the rash was 7 days; Bossard⁷ gives 5 days as the usual duration. In many areas the rash was described as a "punctate erythema"

but was further characterized as being a very bright red in color. Itching of the skin, described as a prominent symptom by some authors, was present in only 1 of these cases (Case 1). Desquamation followed in every case and was most pronounced at the site of application of the ointment. Milian^{11b} states that the desquamation varies directly with the intensity of the eruption and ranges from a light branny flaking to a coarse exfoliation. He points out that it is not accentuated at the fingers and toes as in scarlet fever. It will be noted that 5 of the 8 patients at some time complained of sore throat, making the resemblance to scarlet fever all the more close. In none of the cases in which a blood count was reported was there a leukocytosis, the white counts ranging from 4000 to 7000. The eosinophilia mentioned by some authors was not present in this series. Mercurial stomatitis was present in only 2 of the 8 cases (25%), and this would appear to agree with the observations of Gaumond⁹ and Milian^{11b} who state that cutaneous manifestations of mercurial poisoning are usually not accompanied by mercurial stomatitis. Abnormal urinary findings (mercury in Case 2 and albumin in Case 7) were present only in those patients with mercurial stomatitis and were conspicuous by their absence in the remaining cases.

As regards diagnosis and, above all, the differentiation of these cases from scarlet fever, it would seem that the most helpful points are: 1, a history of recent exposure to mercurials, either by inunction or by injection; 2, the brilliancy of the erythema; 3, helpful laboratory data. The latter would include a negative Schultz-Charlton reaction, absence of leukocytosis, and absence of *beta*-hemolytic streptococci from the throat culture. The character of the rash and the character of the desquamation alone cannot be relied upon. Schamburg¹² has most aptly stated the problem: "It may be asserted that more errors of diagnosis both of commission and omission are made in connection with scarlet fever than with any other common eruptive fever. I am inclined to believe that the more frequent error is made in regarding as scarlet fever some affection accompanied by a scarlatinoid rash. Consciously or unconsciously we attribute more diagnostic weight to the existence of the rash than its importance warrants." And again, concerning desquamation, he says: "It cannot be too strongly expressed and impressed that all that scales is not scarlet. Scaling is the terminal stage of pathological changes in the skin which are by no means peculiar to scarlet fever."

Summary. Eight cases of scarlatiniform erythema with other evidences of systemic reaction are reported and described. Each of these reactions occurred following inunction with blue ointment (33% mercury) in the treatment of pediculosis. Because of the resultant fever and erythema, all of these patients were referred to this hospital with a diagnosis of scarlet fever. Despite the already

numerous reports of hydrargyria occurring after the unrestricted use of this ointment, untoward reactions are still fairly frequent. This is chiefly because the ointment is readily available without prescription and consequently laymen are likely to apply it freely without medical supervision. Caution in its use is advised even in the hands of the physician.

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BOOK REVIEWS AND NOTICES

FROM THIRTY YEARS WITH FREUD. By THEODOR REIK. Translated by RICHARD WINSTON. Pp. 241. New York: Farrar & Rinehart, Inc., 1940. Price, \$2.50.

NEUROPSYCHIATRISTS had long recognized the permanency of distressing memories. Charcot had shown that hysterical manifestations were preceded by emotions due to accidents. Janet had taught that "traumatic memories," directly or indirectly, might later cause neuroses. The influence that these predecessors of Freud may have had upon his work, the author does not comment upon. Breuer, through hypnosis, was recalling in hysterical patients, experiences of which they had lost conscious recollection. Freud began to work with Breuer, but later departed in anger, and adopted "free association" as a better means of reviving forgotten memories. Instead of treating his subject logically, the author is emotionally dominated by his admiration for the Master whose name he believes imperishable, living "long after Hitler and Mussolini are dust." He is not a physician and agrees with Freud that others "had come closer to the fundamental truths of psychoanalysis than had the physicians." One is more nearly in accord with the author when he speaks of the masterful style employed by Freud in his writings, as exemplified in his "Dostoyevsky and Patricide." N. Y.

PSYCHOTHERAPY. Treatment That Attempts to Improve the Condition of a Human Being by Means of Influences That Are Brought to Bear Upon His Mind. By LEWELLYS F. BARKER, M.D., Emeritus Professor of Medicine, Johns Hopkins University; Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 218. New York, D. Appleton-Century Company, Inc., 1940. Price, \$2.00.

THIS small volume for general practitioners and intelligent laymen is by a physician who employs psychotherapy in conjunction with all other remedial measures. The methods of Freud, Janet, Adler, Jung, Rank, Stekel and Meyer are discussed as to their applicability either in functional or organic diseases, and in the various periods of childhood, adolescence, adult life and old age. Environmental and hereditary factors are regarded as of the utmost importance. It is the author's belief that proper psychotherapy will prove of ever-increasing importance. There is an informative glossary, an extensive bibliography and a good index. N. Y.

PLAGUE ON US. By GEDDES SMITH. Pp. 365; illustrated. New York: The Commonwealth Fund, 1941. Price, \$3.00.

A MEMBER of the staff of the Commonwealth Fund writes to other laymen about communicable diseases in a crisp and entertaining, yet clear and accurate, style that should bring heart-searching to many medical writers. Also the medical man as well as the layman will have much to learn from its contents. From the first chapter on the major plagues of history to the ninth and last, the Epilogue, and especially in the Epilogue one is constantly meeting important but generally overlooked facts, fresh points of view, and an occasional pregnant surmise. At a time when war is again causing large movements of the population of this country and severe epidemics

may be awaiting us as they did in 1918, this book's appearance is timely. From it, for instance, we learn almost the latest information about influenza—this is a front that is being pushed forward almost daily—and we are gratified to know that even if we are threatened with another severe epidemic, already we are much better equipped to meet the situation than we were in the last war.

Once more we are indebted to the Commonwealth Fund, both for stimulating the creation of this book and for presenting it to the public.

E. K.

THE JOURNAL OF CLINICAL ENDOCRINOLOGY, VOL. 1, NO. 1, JANUARY, 1941.

Issued Monthly for The Association for the Study of Internal Secretions
Pp. 90; illustrated. Springfield, Ill.: Charles C Thomas, 1941. Price:
annual subscription, \$6.50; single copies, \$1.00.

THIS new journal is the second to be published by The Association for the Study of Internal Secretion. With the rapid growth of this subject in the past quarter century it has become necessary to divide the field, Endocrinology covering the experimental side of endocrine research, the new journal being devoted to the clinical aspects of the subject. The distinguished character of its Publication Board and Editorial Committee gives assurance that a high standard will be maintained. Thus does the romance period of endocrinologic literature recede still further into the obscurity of the past.

E. K.

DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS AND STERILITY.

By CHARLES MAZER, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to the Mount Sinai Hospital, Philadelphia, and S. LEON ISRAEL, M.D., F.A.C.S., Instructor of Gynecology and Obstetrics, School of Medicine, University of Pennsylvania; Associate Gynecologist to the Mount Sinai Hospital, Philadelphia. Pp. 485; 88 illustrations and 1 colored plate. New York: Paul B. Hoeber, Inc., 1941. Price, \$6.50.

IN this volume presented by authors long known for their research in clinical and laboratory phases of endocrinology, the family physicians will find much to help him in the treatment of these frequent gynecologic complaints.

The text, which is divided into 30 chapters, begins with the normal physiology of the female reproductive system. The physiologic contrasts of estrogen and progesterin are well brought out, while the dysfunctions of puberty are well arranged from the standpoint of treatment. The normal menstrual cycle and its phases, and the menstrual hormone balance are well correlated in a discussion of the synchronous changes in this inter-related phenomenon. The authors regard medical treatment of dysmenorrhea with scepticism, but mention agents of worth and include certain indications where insulin may have a beneficial effect. They regard the various types of cervical dilatation as of value only in producing pressure atrophy on nerve ends. Other types of surgery in dysmenorrhea are described. The authors regard low dosage irradiation to the pituitary glands and ovaries as the best treatment for exaggerated pre-menstrual tension. They discuss the physiologic approach in the treatment of migraine which has a close menstrual connection.

The debatable question of pre-menstrual breast changes is analyzed from both points of view. The authors recommend the inhibition of hypophyseal activity, the cause of a mazoplasia, by estrogen. Before proceeding to the subject of amenorrhea, a short section brings out the few known facts regarding vicarious menstruation.

Amenorrhea based on pituitary derangements is discussed at considerable length, and with profuse reference to the literature, under three headings: adiposogenital dystrophy (Froelich's syndrome), pituitary cachexia (Simmonds' disease), and pituitary adenomas. For these three dissimilar conditions there is a full correlation and evaluation of symptoms, physical signs and laboratory examinations, with a very satisfactory outline of treatment.

A similar handling of amenorrhea caused by primary ovarian derangements is followed by series of shorter chapters on the relationship of amenorrhea to dysfunction of the uterus, thyroid glands and both functional and organic derangements of adrenal glands and the nervous system. In considering the subject of hypomenorrhea three types are considered with appropriate therapeutic approaches.

The portion of the book which particularly appeals to the Reviewer and should be of much advantage to the general practitioner, for whom the book is intended, is the section dealing with various abnormal uterine hemorrhages. Each pathologic or functional factor is well described, and its influence evaluated together with means of diagnosis and treatment. Careful perusal of this section of the book and the application of the methods suggested should clear up the etiology of many cases and lead to appropriate and easily managed therapy. The large clinical experience of the authors is well reflected in their description of the dysfunctional bleeding of puberty and the menopause, and the appraisal of the hormonal therapy suggested in the literature, together with their own specific recommendations.

The second part of the book, on Sterility, discusses various pelvic lesions in the female recognized as frequent causes. Tubal patency and uterosalpingography are contrasted as to their value in diagnosis. The endocrine factors and endocrine treatment are well presented. The dual etiology of this condition is recognized in an excellent chapter by the authors on the male factors and equally good chapters on the diagnosis and treatment of male sterility by Dr. Charles W. Charny. It is interesting to note that tubal damage was a factor in 245 cases (55.9%) of their cases, while male infertility was responsible in 182 cases (41.5%). The authors stress the importance of germ plasm defects in the causation of habitual abortion. An interesting feature of the book is the appendix which lists the various commercial preparations of hormones, and their classification and unit values.

Such a fine recapitulation and presentation of the subject should be of interest not only to the specialist in gynecology, but also to the general practitioner. The plan of the book and the manner of presentation should be of special value to the family physician in the aid offered as to diagnosis and in the evaluation of various types of treatment suggested for the symptomatic conditions discussed.

P. W.

DERMATOLOGIC ALLERGY. An Introduction in the Form of a Series of Lectures. By MARION B. SULZBERGER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University; Associate Attending in Dermatology and Syphilology, Montefiore Hospital, New York, etc. Pp. 540; 39 illustrations, 13 colored plates and 17 tables. Springfield, Ill.: Charles C Thomas, 1940. Price, \$8.50.

Modestly called in the preface a primer, an introduction to dermatologic allergy, the volume falls little short of being the book of reference which it specifically claims not to be. Apparently, in committing his lectures to print, the author has allowed them to expand well beyond their original

scope. (One of the "lectures" runs close to 50 pages and would require nearly 3 hours to deliver.) In addition to this formidable dose of material, the troubles of the beginner are increased by a style that is given to excessively long and involved sentences. The Reviewer therefore suspects that a neophyte in allergy would find the book hard going. On the other hand, allergists, whether dermatologists or not, will find it very interesting and stimulating, for the author has taken a broad view of the field and, giving free rein to a vivid imagination, has dared to set down much that is speculative and conjectural, but suggestive of possible lines of development of the subject. Chapter headings include: definitions and classifications; the skin as a protective organ, the recorder and the possible originator of allergic changes; some fundamental phenomena of allergy and their significance; the investigation of individual cases; common allergic skin reactions and skin diseases; eczematous contact dermatitis; urticarial responses to skin tests; urticarial skin diseases, including atopic dermatitis; some manifestations of allergy in infectious diseases; allergy to tuberculin; allergy to fungi; allergy as the basis of cutaneous syphilis; allergy and allergic skin reactions in miscellaneous infections; drug allergy and drug eruptions; the future of allergy. There are appended a translation of von Pirquet's article in which he first proposed the term "allergy"; a list of substances and concentrations for patch testing; a table of criteria for determining the industrial character of a dermatitis; suggestions for the management of eczematous and urticarial dermatoses; a glossary. The illustrations are excellent.

R. K.

THE RÔLE OF THE LIVER IN SURGERY. By FREDERICK FITZHERBERT BOYCE, B.S., M.D., Diplomate of the American Board of Surgery; Fellow of the American College of Surgeons; Visiting Surgeon: Charity Hospital of Louisiana at New Orleans, French, Mercy, and Southern Baptist Hospitals, Hotel Dieu and Touro Infirmary. Pp. 365; 44 illustrations and 25 tables. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.00.

THIS monograph, which was awarded the quinquennial Samuel D. Gross Prize for research in surgery by the Philadelphia Academy of Surgery in 1940, is a worthy successor to the distinguished recipients of this award in former years. In it the author has included a reasonably full review of the literature as well as his own original work and has handled well the difficulties presented by a field which is being opened further almost month by month. The Reviewer received clearly the impression that the author was well aware of the fact that his subject was not static but was undergoing constant change, and felt that by his awareness and resulting comments he would stimulate further studies in this important field.

The monograph reviews the speculations concerning "liver" deaths and the "hepatorenal" syndrome, wisely retaining the quotation marks, but fully covering known means of combating these complications. Tests of hepatic function are discussed and while the Reviewer feels that the author is perhaps too optimistic about the information they afford, he agrees that it is well to use them for what they are worth.

The hepatic factor in thyroid disease and in non-biliary and non-hepatic disease is given the importance that is its due. These chapters should be read carefully by every general surgeon, for too frequently liver injury is considered only in relation to the surgery of the gall bladder and the bile ducts.

Exception must be taken to the author's views on ether irrigation of the common duct. It is not accurate to state that "If the occlusion of the common duct is caused by a stone, gravel or inspissated bile, patency can usually be achieved by introducing into the drainage tube equal quantities

of ether and alcohol (Pribram, 1935) and repeating the irrigation until the occluding substance is dissolved." The Reviewer does not believe with Pribram that irrigation of the common duct with ether is a substitute for careful exploration of the common duct. Certain stones are not dissolved by this method even under the best of circumstances. Lahey in particular has emphasized the necessity of careful common duct exploration in calculous cholecystitis and his results and those of many other surgeons are convincing as to the rationale of the procedure.

If this monograph is read carefully by the general surgeon it cannot help produce a more thoughtful and critical attitude toward the rôle of the liver in surgical disease and should result in the saving of many lives.

I. R.

THE MEDICAL REPORTS OF JOHN Y. BASSETT, M.D. The Alabama Student. With an Introduction by DANIEL C. ELKIN, M.D., Joseph B. Whitehead Professor of Surgery, Emory University. Pp. 62; illustrated. Springfield, Ill.: Charles C Thomas, 1941. Price, \$1.50.

"An Alabama Student," one of the best and best known of Osler's biographic essays, has given John Y. Bassett of Huntsville, Ala., an enduring niche in the medical Hall of Fame. Bassett's two articles in Fenner's rare *Southern Medical Reports*, which led Osler to his study of Bassett, are here reprinted in full, together with Dr. Elkin's Introduction, concerning chiefly Fenner's connection with Bassett. An appendix gives further details of Bassett's life than were available to Osler, in a letter to Osler from Dr. C. H. Mastin, a pupil of Bassett's. Admirers of both Bassett and Osler will be glad to know this attractive little volume.

E. K.

MODERN DERMATOLOGY AND SYPHILOLOGY. By S. WILLIAM BECKER, M.D., Associate Professor of Dermatology and Syphilology, Kuppenheimer Foundation, University of Chicago, and MAXIMILLIAN E. OBERMAYER, M.D., Assistant Professor of Dermatology and Syphilology, Kuppenheimer Foundation, University of Chicago. Pp. 871; 461 text illustrations and 32 full color plates. Philadelphia: J. B. Lippincott Company, 1940. Price, \$12.00.

THE authors have demonstrated their courage and initiative by producing a new type of textbook in the already over-textbooked field of dermatology. This work is written in a discursive and easily readable fashion for the general practitioner and the medical student rather than the specialist. The style is conversational and that of the amphitheatre; the format, in the form of a two-column page, makes for easier reading; the typography is excellent. Too much praise cannot be lavished on the half-tone illustrations, which are surpassingly good, and in a class by themselves. The color plates, however, despite the authors' oath of allegiance in their preface, demonstrate in the Reviewer's opinion exactly the contrary—namely, that color illustration is unnecessary in dermatologic textbooks, an added cost, and diagnostically a common nuisance. The special paper which such style of illustration requires, adds greatly to the physical weight and expense of what should be a convenient handbook.

Sixteen groups of topics in the field of dermatology are covered, and there is a section of 178 pages on syphilis, covering 20 topics. The authors do not profess to be encyclopedic. The dermatologic divisions of the table of contents indicate distinctive and interesting departures from conventional dermatologic textbook classifications, with a trend towards functional, as distinguished from morphologic background. This departure from conventional technique is one that the Reviewer regards as eminently desirable, and one is not therefore disposed to be too harsh with some of the odd juxtapositions which one encounters, as for example, the mixture

of symptoms, causes, and morphologic groups collected under "Papulo-squamous Eruptions" (p. 194). Under "Dermatoses of Physical Origin" one finds factitial eruptions which are expressions of psychoneurogenous functional disturbance. Erythema nodosum accompanies rosacea, a vaso-neurosis; and morphea, also probably a disease of the nervous system, into the category of dermatoses of vascular origin.

This, however, is merely minor criticism. The emphasis on the functional throughout the work, and especially in the liberal space and enthusiastic interest given to the neurodermatoses, is a great advance to which the authors and their group have made notable contributions in literature and thought. Excellent sections, from the standpoint of the student and practitioner especially are those on pyogenic and mycotic infections of the skin. The authors have read into both their diagnosis and therapy many of those valuable practical hints and observational slants which are the best contribution of the individual expert to the commonsense and everyday practice in his field. The general material on anatomy, physiology and immunology is up-to-date, and men trained in the hematoxylin-eosin era of American histopathology especially can afford to read these sections with attention. The diagrams covering the cross-sections of the various elementary lesions of the skin have unusual teaching quality. The formulæ and the directions accompanying them should satisfy both student and practitioner who cannot take the time to indulge in reasoned extemporization. The sections on allergy, somewhat scattered, and the discussion of the toxic dermatoses of epidermal origin are an advance on most texts available in this country. References to the literature through this section of the book are abundant and well chosen. An exasperating phrase, "diagnosis is not difficult" recurs too frequently for a student-practitioner text.

The section on syphilis raises in the Reviewer's mind the question as to whether, in the light of the high degree of specialization that syphilology has reached in the last two decades, this topic should really form a part of dermatologic textbooks. It is impossible to present syphilis satisfactorily to the practitioner and student in a discursive and conversational way. The effect is sketchy and the sharp definition of principles, the precise figures and the now syphilologically accepted rules of procedure are blurred by over-emphasis on visible syphilids and unpardonabilities such as verbal and tabular differentiation on morphologic grounds of the chancre from other lesions on the genitalia. Even in a presentation such as this, though better balanced than the average, the description of *tabes dorsalis* and *taboparesis* occupies a little more than one page, while the picture of *mal perforans* occupies a full half-page. The Reviewer is almost convinced that a modern condensed textbook of diagnosis and treatment in syphilology intended for practitioners and students could be published without any illustrations whatever, and would indeed be the better for the lack. Only the extended and special texts or the single or multiple volume encyclopedia of the disease can afford such indulgence in history, orientation and illustration as is here presented. The differential table of chancre *versus* chancreoid, which if printed at all should be as an illustration of what *not* to do under practice conditions, is not the only example of criticizable syphilology. A fairly careful search disclosed no description of the serologic follow-up of penile lesions, especially chancreoid. The authors have accepted Coöperative Clinical Group results in almost everything else; but in their treatment systems (summarized on a special insert sheet) the internationally and nationally evaluated systems of treatment, for which precise numerical and percentage information as to procedure and results is available, apparently do not appear. In their place are methods of treatment, perhaps meritorious and deserving of consideration, but for which no evidence of perfor-

mance is supplied. Such material and its evaluation belong first in the current literature, and then under review in special texts, but should not form a part of a description of current treatment conceptions, especially in early, latent and congenital syphilis and syphilis in pregnancy, in which more thoroughly evaluated and endorsed procedure should be popularized. The references to the literature in the syphilologic section are not up to the standard of the rest of the work, and there are some mistakes in reference names which should be corrected in future editions. The emphasis on collateral public health and social hygiene factors in the control of syphilis is commendable and especially appropriate to a time of national emergency, with its characteristic venereal disease control problems.

Such critical comment as has been offered should not, however, obscure the fundamental interest and merit of this book. It is a new, courageous attack on the teaching problem of dermatology, embodying many originalities of approach, viewpoint and technique with superlative illustrations and genuine up-to-dateness in many fields such as functional disease, allergy and so forth, which form little or no part of the heretofore conventional texts for dermatologists themselves, not to mention medical students and practitioners.

J. S.

METHODS OF TREATMENT. By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals, and EDWARD H. HASHINGER, A.B., M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals, and St. Luke's Hospital, Kansas City, Mo. With chapters on Special Subjects by 12 Contributors. Pp. 997; 138 illustrations. Seventh edition. St. Louis: The C. V. Mosby Company, 1941. Price, \$10.00.

THE seventh edition of this well-known textbook is planned to furnish an outline of all the methods of treatment employed in internal medicine. The presentation is characterized by unusual clarity and, while the Reviewer's methods would differ from those of the authors in certain particulars, the book is a mine of information useful to anyone practising medicine.

I. S.

BACTERIOLOGY IN NEUROPSYCHIATRY. A Survey of Investigations Concerned With the Specific Rôle of Infections and Immune Processes. By NICHOLAS KOPELOFF, PH.D., Research Bacteriologist, New York State Psychiatric Institute and Hospital, New York. Pp. 316. Springfield, Ill.: Charles C Thomas, 1941. Price, \$4.50.

The purpose of this book, as the author states in the preface, is a presentation of the contributions which bacteriology and immunology have made towards the elucidation of nervous and mental diseases. The book is divided into four parts, dealing with diseases of known etiology with primary involvement, or secondary involvement of the central nervous system, with diseases of unknown etiology and finally with the immunology of the central nervous system. Current ideas and problems concerning etiology, diagnostic methods, symptomatology, immunology, prophylaxis, treatment and so forth are summarized; and an adequate bibliography of recent years is given to substantiate the various discussions. In the field of psychiatric disorders, infectious and toxic agents have frequently been considered as causative factors. Such reports are critically evaluated by the author in the light of present-day bacteriologic and immunologic knowledge. Although the single discussions are rather brief due to the limited size and the scope of the presentation it very well can be used as a reference book.

W. H.

ACCEPTED FOODS AND THEIR NUTRITIONAL SIGNIFICANCE. Containing Descriptions of the Products Which Stand Accepted by the Council on Foods of the American Medical Association on September 1, 1939. Pp. 492. Chicago: American Medical Association, 1939. Price, \$2.00.

EVERY physician is acquainted with the fine work that is being done by the Council on Foods of the American Medical Association. The Council now publishes descriptions of products which had been found acceptable by it, up to the time of going to press. The volume is an encyclopedic work arranged in chapters with a full table of contents and excellent indices; one of these lists the names of manufacturers and distributors; the other is the general index.

The first section concerns the history and purposes of the Council, the scope of its work and certain of its policies regarding fabricated foods. A brief section is devoted to vitamins and vitamin units. Here we find well illustrated the terse, comprehensive style which characterizes the whole volume. No important information seems to be left out and yet one feels that the few lines devoted to each of the vitamins gives a satisfactory description of its composition and uses.

The volume has inestimable value not only for the physician but to all other persons concerned with nutrition. More and more the doctor is consulted with regard to diets and their nutritional qualities. Especially is he likely to be asked about the relative value of one or another of the highly advertized fabricated foods. In this volume are given, briefly, but completely the valid information needed to answer all such questions.

The section on milk and milk products is especially timely and valuable because it is authoritative. One meets every day persons who say they do not believe in pasteurized milk. Nobody knows exactly what this means and especially can it be easily ascertained that the person who makes such a statement does not know what he means. The complete answer to all such primitive assertions is contained in less than seven lines of this volume.

"Pasteurization of Milk.—The pasteurization of milk is a public health measure. The public should demand pasteurized milk for drinking and the use of pasteurized milk in milk products. The dairy trade should universally adopt pasteurization in the interest of public health.

"There is no cogent evidence that pasteurized milk is significantly inferior nutritionally to raw milk."

The only possible criticism that could be offered concerns the size of type that has been employed; it is smaller than we like for general reading. The font appears to be that used in the *Journal* and the material is probably lifted out without being re-set. As a work which will be consulted chiefly for reference, however, this is not a serious objection.

It is difficult to think of any member of the community who would not derive benefit from the use of this volume.

A. H.

TABER'S CYCLOPEDIA MEDICAL DICTIONARY Including a Digest of Medical Subjects—Medicine, Surgery, Nursing, Dietetics, Physical Therapy. By CLARENCE WILBUR TABER and 14 Associates. Pp. 1488; 273 illustrations. Philadelphia: F. A. Davis Company, 1940. Price, \$2.50; thumb-indexed, \$3.00.

BEGINNING 3 years ago as a "Digest of Medical Terms," then enlarged to a "Medical Dictionary" with some 600 pages and about 20,000 words, this work has now grown to be a "Cyclopedic Medical Dictionary" with nearly 1500 pages and over 50,000 words. This brings it up into the class of abridged dictionaries and as such should find a wide field of usefulness. Valuable features of the book include: concise descriptions of diseases, with their diagnosis, symptoms, treatment, diet and nursing; first aid measures; nursing procedures; food analyses and vitamin tables; tabulated anatomic data; and the equivalents in French, German, Italian and Spanish of a series of 373 questions and expressions useful in dealing with patients.

R. K.

FOREIGN BODIES LEFT IN THE ABDOMEN. The Surgical Problems, Cases, Treatment, Prevention: The Legal Problems, Cases, Decisions, Responsibilities. By HARRY STURGEON CROSSEN, M.D., School of Medicine, Washington University, and DAVID FREDERIC CROSSEN, LL.B., School of Law, Washington University, St. Louis. Pp. 762; 212 illustrations, including 4 color plates. St. Louis: The C. V. Mosby Company, 1940. Price, \$10.00.

THE authors have written this book to emphasize to surgeons the danger of leaving foreign bodies in the abdominal cavity, and they outline the best plan of treatment for various types of such cases. They have searched the literature thoroughly and compiled statistics on practically every type of abdominal foreign body which has been reported.

In the first part, on sponges left in the abdomen, the symptoms and signs of this accident are presented and numerous cases cited to show the various end-results which may follow. The various methods of preventing the loss of sponges are mentioned.

Then follow chapters on various other types of foreign bodies, such as forceps, needles and so forth. The final part of the first portion of the book has to do with swallowed foreign bodies and the treatment of these cases.

The second portion of the book concerns the legal aspects of the subject. Various court actions and cases are analyzed. The question of the reliance on the sponge count, the final examination of the operative field and other such questions are discussed.

The book should be an excellent reference work in medico-legal cases and is probably of as much value to lawyers as to doctors. It is well illustrated, with excellent drawings and photographs. L. F.

NEW BOOKS.

America Organizes Medicine. By MICHAEL M. DAVIS, Chairman, Committee on Research in Medical Economics. Pp. 335. New York: Harper & Brothers, 1941. Price, \$3.00.

Studies on Tuberculosis. The Spread of Tuberculosis in Negro Families of Jamaica, B. W. I. By E. JOYCE SAWARD, PERSIS PUTNAM, and EUGENE L. OPIE. *The Fate of Negro Persons of a Tropical Country, Jamaica, B. W. I., After Contact With Tuberculosis.* By EUGENE L. OPIE, PERSIS PUTNAM, and E. JOYCE SAWARD. *A Survey of Tuberculosis Infection in a Rural Area of East Alabama.* By A. W. GRAHAM, P. W. AUSTON, and PERSIS PUTNAM. *The Fate of Persons Exposed to Tuberculosis in White and Negro Families in a Rural Area of East Alabama.* By A. H. GRAHAM, P. W. AUSTON, and PERSIS PUTNAM. (The American Journal of Hygiene Monographic Series, No. 16, February, 1941; financed by The Rockefeller Foundation, New York City.) Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 198; illustrated. Baltimore: The Johns Hopkins Press, 1941. Price, \$1.10.

The New International Clinics, Volume 1, New Series 4, March, 1941. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 17 Collaborators. Pp. 304; illustrated. Philadelphia: J. B. Lippincott Company, 1941.

In addition to 8 original contributions, this number contains 13 "clinics" from the Yale School of Medicine, and a review article on the present status of procedures for the prevention of certain of the communicable diseases.

The Mask of Sanity. An Attempt to Reinterpret the So-called Psychopathic Personality. By HERVEY CLECKLEY, B.S., B.A. (Oxon.), M.D., Professor of Neuropsychiatry, University of Georgia School of Medicine, Augusta. Pp. 298. St. Louis: The C. V. Mosby Company, 1941. Price, \$3.00.

- That None Should Die.* By FRANK G. SLAUGHTER. Pp. 423. New York: Doubleday, Doran & Co., Inc., 1941. Price, \$2.75.
- Manual of Clinical Chemistry.* By MIRIAM REINER, M.Sc., Assistant Chemist to The Mount Sinai Hospital, New York. Introduction by HARRY SOBOTKA, Ph.D., Chemist to The Mount Sinai Hospital, New York. Pp. 296; 18 illustrations and 17 tables. New York: Interscience Publishers, Inc., 1941. Price, \$3.00.
- Masochism in Modern Man.* By THEODOR REIK. Translated by MARGARET H. BEIGEL and GERTRUD M. KURTH. Pp. 439. New York: Farrar & Rinehart, Inc., 1941. Price, \$4.00.
- The Medical Clinics of North America, Volume 25, No. 2, March, 1941—Baltimore Number.* Pp. 303; 21 illustrations. Philadelphia: W. B. Saunders Company, 1941.
- The 11 articles of the symposium in this Baltimore number are about various aspects of legal and industrial medicine. The 9 other "clinics," as usual, cover widely varying aspects of medicine.
- A History of Magic and Experimental Science, Vols. 5 and 6. The Sixteenth Century.* (History of Science Society Publications, New Series IV.) By LYNN THORNDIKE, Professor of History, Columbia University. Pp. Vol. 5, 695; Vol. 6, 766. New York: Columbia University Press, 1941. Price, \$10.00.
- Spermatozoa and Sterility. A Clinical Manual.* By ABNER I. WEISMAN, M.D., Adjunct Gynecologist, Jewish Memorial Hospital; Clinical Assistant, Visiting Gynecologist and Obstetrician, Metropolitan Hospital, New York. With a Foreword by ROBERT L. DICKINSON, M.D. Pp. 314; 77 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, \$5.50.
- The Comparative Physiology of Respiratory Mechanisms.* (The William J. Cooper Foundation Lectures, 1939, Swarthmore College.) By AUGUST KROGH. Pp. 172; 84 illustrations. Philadelphia: University of Pennsylvania Press, 1941. Price, \$3.00.
- Science and Seizures. New Light on Epilepsy and Migraine.* By WILLIAM G. LENNOX, M.D., Sc.D. HON., Assistant Professor of Neurology, Harvard University Medical School; Visiting Neurologist, Boston City Hospital, etc. Pp. 258; 10 illustrations. New York: Harper & Bros., 1941. Price, \$2.00.
- Medical Conferences of the University of Pennsylvania Bicentennial Celebration.* No. D., *A Challenge to Scholarship.* By W. MANSFIELD CLARK. Pp. 20. Price, 50c. No. 16, *Chemotherapy.* By E. K. MARSHALL, JR., JOHN S. LOCKWOOD and RENÉ J. DUBOS. Pp. 42; 6 illustrations. Price, 50c. No. 15, *Modern Aspects of the Antituberculosis Program.* By J. BURNS AMBERSON, KENDALL EMERSON, WILLIAM CHARLES WHITE and LOUIS I. DUBLIN. Pp. 38. Price, 50c. No. 14, *The Relation of Diseases in Lower Animals to Human Welfare.* By JOHN R. MOHLER, RAYMOND A. KELSER and CASSIUS WAY. Pp. 39. Price, 50c. Nos. 6, 7, *Female Sex Hormones.* By EDWARD A. DOISY, PHILIP E. SMITH, ROBERT T. FRANK and ELMER L. SEVRINGHAUS. Pp. 58. Price, 50c. No. 5, *Nutrition.* By CONRAD A. ELVEHJEM, CYRIL N. H. LONG and ELMER V. MCCOLLUM. Pp. 46. Price, 50c. No. 4, *Medical Problems of Old Age.* By LOUIS I. DUBLIN, HOWARD T. KARSNER, O. H. PERRY PEPPER and BARNEY BROOKS. Pp. 46. Price, 50c. No. 3, *Therapeutic Advances in Psychiatry.* By EDWARD A. STRECKER, ABRAHAM A. BRILL, NOLAN D. C. LEWIS, and ARTHUR H. RUGGLES. Pp. 35. Price, 50c. No. 2, *Problems and Trends in Virus Research.* By THOMAS M. RIVERS, WENDELL M. STANLEY, WILBUR A. SAWYER, THOMAS FRANCIS, JR., RICHARD E. SHOPE, JOSEPH STOKES, JR., and GEOFFREY RAKE. Pp. 75. Price, 75c. Philadelphia: University of Pennsylvania Press, 1941.

NEW EDITIONS.

- Diseases Transmitted from Animals to Man.* By THOMAS G. HULL, PH.D., Director, The Scientific Exhibit, American Medical Association, with Fourteen Contributors. Pp. 403; 43 illustrations. Second Edition. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.50.
- A Diabetic Manual for the Mutual Use of Doctor and Patient.* By ELLIOTT P. JOSLIN, M.D., Sc.D., Clinical Professor of Medicine Emeritus, Harvard Medical School; Medical Director George F. Baker Clinic at the New England Deaconess Hospital; Consulting Physician, Boston City Hospital. Pp. 238; 53 illustrations. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$2.00.
- The Avitaminoses. The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases.* By WALTER H. EDDY, PH.D., Professor of Physiological Chemistry, Teachers' College, Columbia University, etc., and GILBERT DALLDORF, M.D., Pathologist to the Grasslands and Northern Westchester Hospitals, Westchester County, N. Y. Pp. 519; 28 illustrations and 40 plates. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$4.50.
- Handbook of Anæsthetics* (Formerly Ross and Fairlie). Revised by R. J. MINNITT (Trinity College, Cambridge), M.D. (LIVERPOOL), D.A. (R.C.P. & S. ENG.), Lecturer in Anæsthesia, University of Liverpool; Director of Anæsthetics, David Lewis Northern Hospital, Liverpool, etc. With Chapters on Local and Spinal Anæsthesia by W. QUARRY WOOD, M.D., CH.M., F.R.C.S.E., Surgeon, Edinburgh Royal Infirmary. Pp. 364; 102 illustrations. Fifth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, \$4.00.
- Physical Chemistry for Students of Biology and Medicine.* By DAVID INGERSOLL HITCHCOCK, PH.D., Associate Professor of Physiology in the Yale University School of Medicine. Pp. 264; 22 illustrations. Third Edition (with laboratory experiments). Springfield, Ill.: Charles C Thomas, 1940. Price, \$3.50.
- Hutchinson's Food and the Principles of Dietetics.* Revised by V. H. MORTAM, M.A. (CANT.), Professor of Physiology at King's College of Household and Social Science, University of London, and GEORGE GRAHAM, M.D. (CANT.), F.R.C.P. (LOND.), Physician to St. Bartholomew's Hospital. Pp. 648; 27 illustrations. Ninth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, \$6.75.
- A Laboratory Manual of Physiological Chemistry.* By D. WRIGHT WILSON, Benjamin Rush Professor of Physiological Chemistry, University of Pennsylvania. Pp. 298. Fourth Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$2.50.
- "Many minor changes have been made to make the manual more satisfactory for the student. Experiments on saliva have been augmented and modified. A short discussion of photoelectric colorimetry has been included." (From Preface.)
- Roentgen Interpretation.* By GEORGE W. HOLMES, M.D., Roentgenologist to the Massachusetts General Hospital and Clinical Professor of Roentgenology, Harvard Medical School, and HOWARD E. RUGGLES, M.D., Late Roentgenologist to the University of California Hospital and Clinical Professor of Roentgenology, University of California Medical School. Pp. 364; 246 illustrations. Sixth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$5.00.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS.

UNDER THE CHARGE OF

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THE TREATMENT OF CIRCULATORY COLLAPSE AND SHOCK.

FAILURE of the circulation results from a variety of causes. The terms "circulatory collapse" and "shock" are applied to circulatory failure in which the heart is not primarily at fault. The heart cannot act as an efficient pump unless the venous inflow to it is adequate; it cannot pump out blood which it does not receive. In peripheral circulatory failure, it is assumed that the venous return is inadequate because of some disturbance in the peripheral circulation and that if the venous return were made adequate, the heart would function normally. Since many circulatory failures affecting the body as a whole which are not the result of inherent weakness of the heart muscle have been included under the term "shock," it is not surprising that authors writing on the subject have had difficulty in finding a definition of shock that satisfies all the workers in the field.

From the physiologic viewpoint, peripheral circulatory failure may be said to be present whenever the blood flow to the tissues becomes inadequate in the presence of a heart capable of sustaining a normal blood flow. From this definition, it is immediately obvious that the clinical picture of peripheral circulatory failure will show considerable variation, depending upon the etiology of the circulatory failure and upon the nature of the many compensatory reactions which may occur in the body. Homans¹⁷ summarizes the clinical picture of shock as follows: "(1) An appearance of pallor, sometimes associated with slight cyanosis; (2) a cold, moist, or sweaty skin; (3) a rapid, regular but thready pulse; (4) rapid, usually shallow respiration; (5) restlessness and an appearance of anxiety which may change under unfavorable circumstances to dulness and lessened sensitivity; (6) thirst; (7) a variable amount of nausea and sometimes vomiting." To this picture there are many exceptions.^{9,26,36b} Some patients do not show pallor or lividity; in others the blood pressure is well maintained; in still others

the heart rate is not increased—indeed, it may be slower than normal. In other patients mental dulness may be absent. Thirst is quite commonly absent. The rectal temperature may be elevated.

In the literature there is frequently no clear-cut distinction made between collapse and shock.⁹ It has been suggested that the terms “primary shock” or “collapse” be applied to sudden short-lived insufficiency of the peripheral circulation, and that the terms “secondary shock” or “shock” be used when the circulating insufficiency is more prolonged.^{5,8,11,36b} This distinction has not been in general use. Nevertheless, it is a useful one, because the prognosis and therapy of sudden transitory insufficiency of the circulation is frequently different from that of more prolonged peripheral circulatory failure. The term “collapse” is preferred to “primary shock” because it is more general. Primary shock associated with wounds is one type of collapse. In this paper, the term “peripheral circulatory failure” will include all examples of generalized circulatory failure in which the heart is capable of functioning normally. “Circulatory collapse” will include all forms of sudden, short-lived peripheral circulatory failure; “shock” will include the cases of peripheral circulatory failure of longer duration.

The Mechanism of Peripheral Circulatory Failure. Investigators agree that the fundamental mechanism of peripheral circulatory failure is a disproportion between the circulating blood volume and the size of the vascular bed.^{5,8,27,31,36b} This disproportion may occur in two ways: 1, because of a decrease in the circulating blood volume so that the vascular bed is not filled; and 2, because of an increase in the size of the vascular bed so that the normal blood volume does not fill the dilated vascular bed. This vasodilation may result from fever, infection, drugs, or it may be of reflex origin. In any case, the venous return to the heart becomes inadequate and the cardiac output decreases.

Circulatory Collapse. Acute transient peripheral circulatory collapse is very common.^{23,36a} It may occur in normal subjects at the sight of blood, during a venipuncture, or if the subject is hurt or becomes nauseated. It frequently occurs in ambulatory patients who have had a cold or infection; in the hospital it is seen in patients with pneumonia or other infections who sit up to use the bed-pan, or in persons who stand up too soon after a bout of fever or after the loss of blood. It occurs from time to time when acutely ill patients are moved, or it may be precipitated by palpation of a tender abdomen. Regardless of the precipitating cause, the clinical picture is the same. The patient becomes deathly pale, breaks out in a cold sweat, and complains of epigastric distress and nausea. The field of consciousness becomes narrowed, objects become hazy and dark, and the subject may lose consciousness. At the onset of the attack, the heart rate usually becomes rapid, but as the arterial pressure falls, the heart rate frequently decreases. At the height of the collapse, the heart rate may be approximately 40 and the radial pulse impalpable. If the subject is held in the upright position, he may develop clonic movements of the arms and legs.

Circulatory collapse in these cases results primarily from pooling of blood in a dilated circulatory bed.^{36a} The blood volume is not decreased in the normal subject with circulatory collapse precipitated by unpleasant visual stimuli, pain or nausea. The marked fall in arterial pressure

indicates that the peripheral vascular bed has dilated so that the normal blood volume no longer fills the dilated vascular bed and the venous return to the heart becomes inadequate. There are two factors operative in this type of collapse. The first one is gravity; the second is the stimuli to the central nervous system. When the patient is in the upright or sitting position, the venous pressure in the parts of the body below the heart is increased by the force of gravity. This increased venous pressure makes the cross-section area of the venous bed below the heart larger when the patient is in the upright position than when he is in the recumbent position. When the tone of these vessels below the level of the heart is suddenly decreased as a result of stimuli from the brain, the blood drains into the dilated vessels, the venous return to the heart becomes inadequate and arterial pressure falls precipitously. The resulting cerebral anoxia may produce unconsciousness.

In the circulatory collapse induced by sodium nitrite^{37,38} or by infection,³² the same two factors are operative, namely, the force of gravity and the relaxation of the venous side of the circulation. In these cases the loss of venous tone is probably the result of the action of the drug, or of the infection, on the veins and venules. Under such circumstances, when the patient is in the upright or sitting position, more than the normal amount of blood is pooled in the relaxed venous system and circulatory collapse may result. Studies of this type of circulatory collapse have shown that the arterioles are constricted to compensate for the decrease in effective blood volume, and that further arteriolar constriction by drugs is not helpful.^{32,39}

If the blood volume is decreased by hemorrhage, vomiting, or loss of plasma into the peritoneal cavity, circulatory collapse may occur when the patient sits up. In these cases the venous tone may not be decreased. When the patient is in the erect or sitting position, the shifting of a normal amount of blood into the lower portion of the body may decrease the venous return to the heart sufficiently to produce circulatory collapse.

In certain patients a similar type of collapse occurs in the recumbent position. Subjects who are bled when they are in the recumbent position may develop collapse which lasts for only a short time, and from which they may recover without any demonstrable increase in blood volume.¹² Palpation of the abdomen in a patient with acute pancreatitis may repeatedly precipitate collapse. In these patients the development of collapse may be of more serious import than in patients in whom circulatory failure is precipitated by gravity.

Patients frequently develop circulatory collapse after spinal anesthesia.^{10,24,30} This is the result of vascular relaxation in the lower extremities and splanchnic areas. This relaxation includes the arterial as well as the venous side of the circulation. The dilated vascular bed pools blood and decreases the venous return to the heart.

In the treatment of circulatory collapse, it is important to make use of gravity in aiding the venous return to the heart. The patient is placed in the recumbent position, and if possible, the foot of the bed is elevated. In most instances this will produce a rapid increase in the arterial pressure and the pulse will become of good volume. The slow pulse which is frequently observed at the height of collapse is the result and not the cause of collapse.^{23,36a} It is of vagal origin and is

caused either by reflex stimulation or by direct stimulation by anoxemia of the vagal centers in the brain. Atropine will prevent slowing of the pulse but will not prevent circulatory collapse.²³ In the treatment of collapse which may occur soon after the induction of spinal anesthesia, the head-down position is contraindicated if the anesthetic used has a specific gravity greater than that of the spinal fluid. The Trendelenburg position may be used, however, after sufficient time has elapsed to allow most of the anesthetic drug to be fixed in the tissues.³⁰

Drug therapy is frequently not needed because recovery may be quite rapid. In patients with severe infection or with a considerable decrease in blood volume, recovery of the circulation may be much slower. If pain is present, morphine sulphate in 15 mg. doses is useful. Except in collapse occurring during spinal anesthesia, the arterioles are usually constricted, and drugs which accentuate this constriction without increasing the venous return are usually ineffective in preventing the onset of collapse.^{33,39} In laboratory experiments,¹⁹ paredrinol sulphate, a drug that increases the venous tone, when administered in doses of 25 mg. intramuscularly or 30 to 50 mg. orally, has been effective in preventing the onset of this type of collapse. Epinephrine and pitresin were ineffective.^{33,39} During spinal anesthesia, ephedrine sulphate, given subcutaneously in doses of 25 to 50 mg., is at least partially effective in preventing a drop in blood pressure.²⁴ Altschule and Gilman¹ have reported that paredrine given intramuscularly in doses of 10 to 20 mg. is likewise effective in preventing a drop of blood pressure during spinal anesthesia.

Shock. More prolonged failure of the peripheral circulation produces the classical clinical picture of shock. In collapse, the duration of the circulatory insufficiency is short; in shock, it is more prolonged.^{8,36a,b} It is generally agreed that in shock the circulatory failure is frequently related to a decrease in blood volume as a result of external hemorrhage, dehydration, or loss of plasma into the peritoneal cavity or into traumatized tissues. In addition, many observers believe that infection and the breakdown products from injured tissues play an important rôle, not only in causing pooling of blood by vasodilation, but also in producing a decrease in plasma volume by increased capillary permeability. There are several monographs which give good reviews of the current opinions on etiology of shock.^{5,8,27,31}

From the clinical point of view, it is essential to remember that the infection must be prevented if possible, and that if present it must be combated with all the means at our disposal. In addition, the blood volume must be kept at an adequate level. Hematocrit determinations and serum protein determinations on venous blood collected without stasis are useful in following cases of hemorrhage, trauma, peritonitis, burns, diarrhea, vomiting, and intestinal obstruction. The protein concentration can easily and quickly be calculated from the specific gravity of the serum by the falling drop method.^{2,18,31} In simple dehydration, which is present in patients with diarrhea or vomiting, there is a rise in the hematocrit reading and in the protein concentration of the plasma. After hemorrhage there is a decrease in both the hematocrit reading and in the protein concentration. If a fluid rich in protein is lost from the blood stream, the hematocrit reading rises and the protein shows only a slight increase, or it may even

fall. This may occur in burns, peritonitis or trauma. If hemorrhage is complicated by dehydration, the hematocrit reading may be low and the protein concentration increased. In essence, an attempt is made to keep the hematocrit reading and protein concentration of the blood within normal limits. They must both approach the normal at the same time. For example, after a severe burn, the hematocrit reading may be very high and the protein concentration normal. If the hematocrit is restored to normal by the intravenous injection of saline, the protein concentration will be too low. Such patients need protein as well as fluid.

In acute infections the blood volume is usually not decreased unless the patient is dehydrated. If the patient's kidney function is normal, dehydration will not occur if sufficient fluids are given to keep the urine specific gravity below 1.012. In such cases no further information as to the state of hydration will be obtained from a knowledge of the hematocrit reading or protein concentration.

The importance of the laboratory aids in maintaining an adequate blood volume has been recently reëmphasized by Scudder.³¹ These laboratory tests are important because they demonstrate the changes in blood volume before they can be detected by clinical observations. It has long been recognized that the fall in arterial pressure may be a late sign in peripheral circulatory failure. As the blood volume decreases, the pressure may be maintained by peripheral arteriolar constriction. In this way, the blood flow to the tissues may be inadequate in the presence of a normal blood pressure. If the arterial pressure falls in spite of peripheral constriction, the prognosis is grave unless the pressure can be raised. In certain instances associated with infection, the arterial pressure may fall primarily as the result of vasodilation. In these patients the peripheral flow may remain adequate and the prognosis is better.^{32,36b}

If hemoconcentration is present, as indicated by a rise in both the hematocrit reading and protein concentration, the fluid intake should be increased either by mouth or parenterally. In these cases normal saline is adequate. If hemorrhage has occurred, transfusions of whole blood are indicated. Unless the anemia is profound, or unless there is concomitant lung disease, it is more important to restore the volume of blood than to restore the erythrocyte concentration. Therefore, even after moderately severe hemorrhage, plasma may be as satisfactory as whole blood in restoring the circulation. Although after hemorrhage physiologic saline may produce a lasting improvement in the clinical signs and symptoms, the blood volume will remain decreased until the body has added protein to the plasma.¹²

In cases in which protein is being lost into the tissues or into the peritoneal cavity, as indicated by an increase in hematocrit reading out of proportion to the rise in protein concentration, saline is not effective in maintaining a normal blood volume because of its diffusibility.³ The fluid added to the blood stream must contain either protein or a substance that is not diffusible through the normal capillary walls and that has an osmotic pressure comparable to that of the normal plasma proteins. Whole blood or plasma are the ideal fluids. In civilian life whole blood has been satisfactory. Recently much work has been done on the use of serum and plasma transfusions in

shock.^{6,20,22,25,29,34,35} Experimental work has indicated that serum and plasma are satisfactory in maintaining the blood volume. Both serum and plasma can be preserved by drying them from the frozen state ("lyophile" process).^{13,15} It has been suggested that the reactions following the intravenous administration of "lyophile" serum are the results of the use of serum and not of a change induced by the process of desiccation. "Lyophile" plasma produced no reactions.³⁴ Other authors state that plasma and serum can be used interchangeably and that properly prepared serum does not produce reactions.^{4,16}

Strumia, Wagner and Monaghan³⁴ have recently summarized the advantages of citrated blood plasma as follows: "(a) It can be readily prepared and safely transported, (b) it can be stored for an indefinite period of time, (c) it is entirely safe and free from reactions, (d) it can be used in large and repeated doses, (e) it is ready for instant use, and (f) it does not add to concentration of erythrocytes if this condition is present."

It is generally agreed that pooled plasma or serum can be given intravenously without typing. Levinson and Cronheim²¹ observed that large pools of serum never showed rich agglutinin content, whereas many of the individual serums that made up the pool possessed a high agglutinin titer. They concluded that there is neutralization of agglutinins *in vitro* when different groups of serum are mixed, and they suggested that serum or plasma prepared for transfusion be made up of pools containing all blood groups. In addition, they stated that neutralization of agglutinins by both tissue and serum of the recipient provides a wide margin of safety in protecting the recipient's red cells from the infused agglutinins.

Cannon⁸ emphasizes that in traumatic shock, in contrast to collapse, there is little or no improvement from elevation of the foot of the bed. This is true in many cases of shock, but not in all. Patients in shock in whom the arterial pressure is maintained by peripheral vasoconstriction are very prone to sudden episodes of circulatory collapse associated with pain or change in position. Elevation of the foot of the bed in these patients will immediately result in an improvement in the clinical picture.

All observers in the World War⁸ emphasized the importance of keeping the patient warm and, in the case of broken bones, the necessity for splinting and immobilization before moving the patient. In civilian practice, the importance of treating shock before moving the patient for Roentgen ray examination or before undertaking any operative procedure is universally recognized. Cannon⁸ stresses the importance of restoring the blood volume before using an anesthetic, and points out the danger of even slight anoxemia in cases of shock. In his experience with patients in shock, ether was a more dangerous anesthetic agent than nitrous oxide and oxygen.

With the exception of morphine for the relief of pain, drug therapy has not proved to be very useful in the treatment of shock. Paredrinol and ephedrine, which have proved to be useful in collapse, have not been shown to be of definite value in shock. Neither epinephrine nor pitressin has been useful in either clinical or experimental shock.⁵ In patients with respiratory depression, coramine and caffeine have proved to be useful as respiratory stimulants, but they have not been shown

to have much effect on the circulation itself. Strychnine has been recommended from time to time, but its usefulness has never been clearly demonstrated in cases of shock. More recently desoxycorticosterone acetate or extracts of the adrenal cortex have been used in the treatment of shock.^{14,28,31,40} While it is clear from experimental work that adrenalectomized animals have a decreased blood volume and may have peripheral circulatory failure, evidence is lacking to prove that patients in shock are deficient in cortical hormone. As yet there are no clear-cut experiments demonstrating that cortical extract of the adrenal glands or desoxycorticosterone is useful in the treatment of shock, except in those cases in which the adrenal cortex is clearly deficient, *i. e.*, in adrenalectomized dogs or in subjects with Addison's disease.

The slow circulation and prolonged tissue anoxia produce the following secondary changes in the body:⁸ the venous blood contains little oxygen; the carbon dioxide combining power is reduced because of tissue acidosis; the basal metabolism is decreased. The changes in serum potassium reported by Scudder probably belong in this group.³¹ In the past, treatment of these secondary changes has not been successful. Recently Boothby, Mayo and Lovelace⁷ have reported that the administration of 100% oxygen is a useful adjunct in the treatment of shock.

Terminal Circulatory Failure. If trauma is severe enough, or if infection cannot be controlled, the circulation eventually fails, regardless of treatment. In this terminal picture, hemoconcentration plays little part because it will occur even if the blood volume is maintained by continuous transfusion. The relative importance of the central nervous system, of the peripheral vascular system, and of the heart in this terminal picture is not clear. This problem needs to be elucidated by more clinical observations.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 18, 1941

Action of Crystalline Pepsin on Diphtheria Antitoxin and Pneumococcus Antibody from the Horse. A. M. PAPPENHEIMER, JR., and MARY L. PETERMAN (Department of Bacteriology, University of Pennsylvania, and Department of Pharmacology, University of Wisconsin). Purified antitoxic pseudoglobulin of high antitoxin content was digested with crystalline pepsin at pH = 4.2 and the specific precipitate formed with pure diphtheria toxin was dissociated with crystalline pepsin according to the methods of Pope (*Brit. J. Exp. Path.*, 20, 132, 201, 213, 1939). The normal antitoxin molecule undergoes the following changes upon digestion with the enzyme: 1, the molecular weight changes from 184,000 to 113,000; 2, the splitting occurs in a plane normal to the long axis; 3, the digested molecule combines with 45% more toxin per milligram than the normal antitoxin; 4, the carbohydrate content of the digested molecule is about 45% higher than normal antitoxin.

Several euglobulin preparations of horse pneumococcus antibody of various types, examined in the standard Svedberg oil turbine ultracentrifuge, showed wide variations in sedimentation constants. The basic unit of pneumococcus antibody in the horse appears to have the same sedimentation constant as normal serum globulin but the molecule tends to aggregate end to end. The amount and extent of aggregation varies in different animals. Both heavy and normal size antibodies have been broken down with pepsin by the method of Graber (*Compt. rend. Soc. de Biol.*, 207, 807, 1938). The digested antibody combines with about twice as much polysaccharide per milligram as the normal antibody and has a sedimentation constant of 5.2×10^{-13} cm./sec./dyne, suggesting a molecular weight less than 100,000. Pepsin-digested horse pneumococcus antibody is quite soluble in water and is

not precipitated by dialysis against distilled water to the same extent as is the normal antibody. It is also soluble in 0.35 % saturated ammonium sulphate in contrast to normal antibody, but may be precipitated by half saturated ammonium sulphate. Almost all preparations were analyzed quantitatively for antibody content by the methods of Heidelberger and Kendall (*Bact. Rev.*, **3**, 49 1939) and in many cases salt-dissociated antibody of high immunological purity was studied.

Effects of Direct Chemical Stimulation of the Respiratory Center. JULIUS H. COMROE, JR. (Department of Pharmacology, University of Pennsylvania). In an attempt to localize the respiratory center by means of a natural chemical stimulus, minute amounts (2 c.mm.) of chemical substances were injected directly into the brain stem in 80 cats through a fine steel needle, 0.5 mm. outside diameter, fixed in the Horsley-Clarke stereotaxic instrument.

The chemical stimulus employed was a 1.3 % solution of NaHCO_3 in distilled water, buffered with CO_2 to pH 7.4 so as to have a CO_2 tension of 250 mm. Hg. The typical response to this solution was an immediate increase in both rate and depth of respiration; control injections of hypertonic or hypotonic saline and distilled water produced no response. More than 750 injections of this CO_2 -bicarbonate solution were made in the pons and medulla up to the level of the inferior colliculus; consistent responses were obtained only in the medulla in the region of the formation reticularis. These experiments add strong confirmation to previous localizations obtained by other methods (electrical stimulation, progressive sectioning of pons and medulla).

Other substances injected were HCl and lactic acids (N/1000, N/100, N/10) which rarely led to respiratory stimulation and then only minimally; saline solutions, equilibrated with CO_2 at 70, 300 and 700 mm. tension, which never stimulated; and 1.3 % NaHCO_3 solutions (unbuffered, pH 8.0), which stimulated regularly.

Since (a) the failure of acid to stimulate cannot be attributed always to cell destruction (for, in some instances, CO_2 -bicarbonate solution injected at the same point a minute later produced definite hyperpnea), and (b) high CO_2 tensions alone do not stimulate, it is suggested that the characteristic stimulus to the respiratory center is not "intracellular acidity" as is currently believed, but rather the HCO_3 ion, acting either by itself or in combination with CO_2 .

Estimation of Total Base in Serum by Means of Measurements of Conductivity and Specific Gravity. F. WILLIAM SUNDERMAN (Department of Research Medicine and the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania). Analyses of the [total base] in serum were correlated with measurements of the conductivity and specific gravity of the serum. The conductivity measurements were made by means of a modified "sugar-ash" bridge utilizing a 60-cycle 110-volt alternating current and a special type of pipette cell. From a statistical analysis of the three variates by partial regression the following formula was derived:

$$\text{Total Base /mEq per L} = 8.62 \text{ SpC} + 0.06 \text{ G} + 27.26$$

where SpC represents the specific conductivity and G is equal to (specific gravity $20^\circ/20^\circ - 1.0000$) 10^4 .

The standard deviation of the percentage differences between the calculated and analyzed values for total base in serum calculated from 46 observations is 1.9. The method is so simple and economical of both time and material that it would seem to afford a method of choice for clinical studies.

Pituitary-Diabetes in the Cat Treated by Low Diet, Insulin and Phlorhizin. F. D. W. LUKENS, F. C. DOHAN and M. W. WOLCOTT (The Cox Institute, University of Pennsylvania). Pituitary-diabetes in the cat has been described in a preliminary report. It was found that if insulin treatment was begun within the first 3 months of diabetes (when the islands showed hydropic degeneration), morphological restoration of the islands and functional recovery of the animals occurred. Recovery by means of insulin was not limited by the severity of the diabetes, but only by its duration, *i. e.*, by the development of irreversible lesions of the islands such as atrophy and hyaline change.

The response of diabetic animals to a reduction in diet has recently been observed. Two cats with very mild diabetes have recovered after 24 and 26 days on a low diet. On resuming the full diet they gained weight and the blood sugar remained normal. On the other hand, 5 cats with moderately severe diabetes have not been controlled by a similar reduction in diet. In contrast to insulin, dietary treatment is greatly limited by the severity of the disease. Finally, 2 diabetic cats have recovered following the administration of phlorhizin in moderate dosage for 2 to 3 weeks. The similarities and differences of these three experimental conditions (low diet, insulin, phlorhizin) have been considered. They permit an analysis of the gross conditions essential to the recovery of hydropic islands of Langerhans and of early diabetes.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JUNE, 1941

ORIGINAL ARTICLES.

POSSIBLE ADAPTATION TO A LOW VITAMIN B₁ INTAKE.*

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THE Netherlands East Indies seem to be a suitable place for the study of subclinical vitamin B₁ deficiencies on historical grounds, as well as from the point of view of the number of cases. Beriberi appears regularly in these countries, although even if not everywhere of equally frequent distribution. Thus one would expect that the subclinical form of the disease would belong to the daily bread of the medical practitioner. This is not so. The chapters on beriberi in the classical textbooks of tropical diseases are, in their absence of descriptions about conditions of pre-beriberi, illustrative of this fact that seems strange at first sight. Very little therein is said about vitamin B₁ deficiencies *sine* beriberi and not even all authors describe the appearance of constipation as an introductory symptom of the disease. The conception of a subclinical vitamin B₁ deficiency has its origin in some of the temperate parts of the world, chiefly in the United States, and the present writer is confident that many practitioners in the tropics must have been much astonished at the long list of symptoms which, according to Williams and Spies,¹⁵ may be attributed to this condition.

Meanwhile I have elsewhere formulated the suggestion that subclinical pellagra might be held partly responsible for these symptoms;⁸ and pellagra is very seldom seen in the Netherlands East Indies.

Since the quantitative estimation of thiamin in blood and urine became possible, a more concrete and less subjective way was given

* At the author's suggestion, this article is being published without submission to him for corrections, in view of present uncertainties of postal communications.—EDITORS.

to investigate the possible significance of subclinical beriberi for these countries also.

In 15 healthy estate laborers, all men, on a standardized diet containing 1.5 to 2 mg. thiamin daily, the output of thiamin in the urine has been estimated during 1 to 3 consecutive days; in 14 of these test persons, subcutaneous test doses of 2 to 4 mg. daily were given in addition, for 2 or 3 days. No exact information was available as to the thiamin content of the diets before the test period. However, even a superficial knowledge of the feeding habits of the population involved gives every reason to assume that the last mentioned diets will have contained considerably less thiamin as compared with those of the test period; probably between 0.6 to 1 mg. *per diem*.^{13b} It may be stated further that the carbohydrate-fat-calorie ratio of the normal diet of the group under consideration is not very favorable in relation to the quantity of thiamin necessary to avoid a deficiency. These diets contain a very high amount of carbohydrate (rice, nowadays very often mechanically polished to a high degree), with low amounts of proteins and fats. That same ratio was contained in the standard diet also: unpolished rice 500 gm., coconut oil 5 gm., dried salted fish 60 gm., and green vegetables 50 gm.

The thiamin outputs could be compared with those of 6 control cases. Three of these, all Chinese, had a mild form of beriberi. The other 3, healthy Javanese, had been prepared beforehand with a diet rich in vitamin B₁, which contained from 2.5 to 3 mg. thiamin and in which the amount of fat was raised to 20 to 25 gm. daily by the addition of 15 gm. red palm oil. This preparatory period had lasted 17, 8 and 10 days respectively.

The output of thiamin* was estimated from the amount in 150 cc. of the assembled 24-hour urine, with the thiochrom method of Westenbrink and Goudsmit.¹⁴

The results are given in the accompanying table. They give rise to the following conclusions: in the healthy test persons the daily output of thiamin was found to be from 0 to 63 micrograms. Eight times, in 5 persons, no thiamin was found at all. The percentages of the subcutaneous test doses excreted were found to be from 2% to 50%, mostly 10% to 30%, corrections having been made by subtraction of the spontaneous outputs. The highest percentages occurred in all but 1 (Protocol No. 8) of the individuals, who showed a relatively high spontaneous output also. However it must be stated that this correlation, on the whole, was not very definite.

In general, the spontaneous output of thiamin was considerably lower than in investigations from the temperate parts of the world, where figures are given that fluctuate between 40 and 300 micro-

* The thiamin was absorbed with frankonite locally. The absorbates were sent by airmail to the Eykman Institute in Batavia, Java, where the estimations proper were made, through the kind coöperation of Dr. A. G. van Veen.

grams,^{2,6,7,10,12,14} although it must be said that absence of any thiamin output also has been encountered there.^{3,7,11} Thus our own figures are highly suggestive of a low vitamin B₁ level in the body. Notwithstanding this low level, the fractions of the test doses excreted are well in accordance with those encountered in Europe and the United States. One is inclined to think that the low level of the vitamin in the body in this country seems to result in approximately the same degree of "saturation" as the higher level from elsewhere.

TABLE 1.—THIAMIN EXCRETION PER DIEM.

No. of protocol.	Spontaneous excretion (in micrograms).			Average (in micro- grams).	Excretion of test doses in %.			Excretion after test doses			
	Days.				Days.			(In micro- grams.)		Of sum of test doses in %.	
								Days.			
1.	2.	3.	1.	2.	3.	1.	2.				
Healthy unprepared persons.											
1 . .	53	—	—	—	32	50	47.5	233	—	3.0	Thiamin.
2 . .	7	—	—	—	11	14	—	13	—	0.1	3 x 2 mg.
3 . .	13	—	—	—	16	15	18	20	—	0.1	2 x 2 "
4 . .	0	—	—	—	3	2	—	0	—	0	3 x 2 "
5 . .	19	—	—	—	16	36	33	158	—	2.3	2 x 2 "
6 . .	8.5	39	43	30	17	23.5	—	123	87	1.2	3 x 2 "
7 . .	0	0	—	0	11.5	20	—	177	213	6.4	2 x 4 "
8 . .	50	13	53	39	12.5	23	24.5	230	153	2.5	2 x 4 " *
9 . .	0	17	0	6	18	25	26	327	163	4.0	3 x 4 "
13 . .	41	27	30	33	31	36.5	43	160	97	1.6	3 x 4 "
14 . .	0	0	13	4	17	16	23	60	70	1.0	3 x 4 "
15 . .	47	23	—	35	—	—	—	—	—	—	None
17 . .	7	17	0	8	15	32	28	237	140	3.0	3 x 4 "
18 .	27	20	40	29			3	.6%			1 x 12 " †
19 .	47	63	57	56			50	.0%			1 x 15 " ‡
Healthy prepared persons.											
12 .	73	67	80	73	25	29	28	203	180	2.0	3 x 4 " §
20 . .	60	57	57	58	30.5	42	38	227	280	3.3	3 x 4 " §
21 . .	0	10	33	14	14.5	5	21	147	110	2.0	3 x 4 " **
Cases of mild beriberi.											
10 . .	3	0	—	1.5	11	7.5	3	0	133	1.0	33 x 4 "
11 . .	0	170	0	57	4	5	17	63	80	0.3	3 x 4 "
16 .	0	0	0	0	11.5	2.5	27	60	0	1.5	3 x 4 "

* Thirty-third day after last test dose, output was 123 micrograms.

† Excretion measured during 4 days.

‡ Excretion measured during 5 days.

§ Diet rich in vitamin B₁ during 20 days.

§ Diet rich in vitamin B₁ during 11 days.

** Diet rich in vitamin B₁ during 13 days.

This point of view receives confirmation from the results in 2 of the prepared control persons. Protocols Nos. 12 and 20 show outputs which are only slightly more than the others and with test dose excretions that are in accordance with the higher ones in the

unprepared individuals. No. 21, however, forms an exception, fully obscure in its cause, whose values approach those of the 3 beriberi cases. This case provides a warning and should prevent too definite interpretations of investigations of this kind. The significance of such exceptions is emphasized by Sciclounoff¹¹ in Europe and in this country by Pannekoek and van Veen⁹ in studies on the vitamin B₁ level in the blood. Melnick and coworkers⁷ admit that a low spontaneous output, from 0 to 60 micrograms, may occur in healthy individuals, but on condition that their diets have been very deficient in vitamin B₁, during and only shortly before the test period. According to these investigators, the fraction of extra test doses excreted will then be found to be from 10% to 20%. With excreted fractions of less than 10%, the test person would be more or less deficient. Their results, however, do not agree either with the clinical condition of our own test persons, or with the vitamin B₁ content of the diets used.

Now it cannot be emphasized too strongly that a low vitamin B₁ level of the body should not be confused with a deficiency in the clinical sense of the word, so long as a definite parallel is not established between the two. Elsewhere⁸ I have given the description of a *clinical* test for tracing conditions of subclinical vitamin B₁ deficiencies in individuals who seem to be in perfectly good health. This test is based on the fact that the rise in systolic blood pressure, which occurs after an injection of epinephrine, becomes much greater after the test person has been first prepared with thiamin, but only in cases that are deficient. With this test a condition of deficiency could be disclosed in the 3 beriberi cases, in the test persons 2, 7 and 14 of the unprepared individuals, but in none of the 3 prepared control persons. A comparison of these results with the thiamin values shows clearly that a definite correlation between the two does not exist and that a low thiamin level does not mean necessarily the existence of a deficiency.

The fact remains significant, of course, that the spontaneous outputs in our small series were considerably lower as compared with the average of the observations from other parts of the world. The reason cannot be other than a lower vitamin B₁ level of the body in our Javanese. This low level in turn must be the outcome, either from a lower intake, or from a lower storage capacity of the body. Now van Coevorden,¹² in Jansen's laboratory, has established exactly that the individuals with a low intake present a lessened capacity to store the vitamin.

The modern feeding habits of many races in the Netherlands East Indies make a low vitamin B₁ intake very probable.^{13b} As has been stated before, the carbohydrate-fat-calorie ratio is not very favorable either. As a rule the inhabitants do not acquire beriberi on these diets. Even conditions of subclinical beriberi are seen much less frequently than one would expect. Van Veen^{13a} thinks that an intake of not more than 0.6 mg. thiamin prevents the appearance of

the disease with certainty. On the other hand, it should be mentioned that 4 of the 5 test persons of Jolliffe and coworkers⁴ acquired objective as well as subjective symptoms of a deficiency in less than 14 days, after the vitamin had been reduced in their diets from 2.5 to 0.5 mg.

All this suggests the consideration of a possible adaptation to a long-standing low vitamin B₁ intake. Anna Láncoz⁵ claims that she has already produced such an adaptation experimentally in hens. A confirmation of her experiments seems highly desirable and of great importance. In human lesions, too, Fabry¹ who works in French Indochina has said, as far back as 1934, that "a great number of persons have only the inapparent form of beriberi" in which "the body installs itself in its dystrophy and lives with it."

If this point of view could be confirmed more definitely as it was possible in the outline given above, this would certainly open wider fields of investigation.

Summary. In a small series of healthy Javanese test persons, under standard conditions, thiamin outputs were found that are considerably lower than the average found in the more temperate parts of the world.

The daily output of thiamin in the population here concerned often does not produce figures that are sufficiently unequivocal to judge, whether in individual cases a condition of deficiency is present or not.

A low vitamin B₁ level of the body should not, without further evidence, be associated directly with a deficiency in the clinical sense of the word.

The vitamin B₁ intake of the population under consideration is very probably much less than the average intake in other parts of the world and on a level which may produce clinical symptoms of deficiency in white people, under experimental conditions.

It is suggested that a chronic low vitamin B₁ intake produces an adaptation of the body.

My thanks are due to Dr. A. G. van Veen, head of the Chemical Department of the Eykman Institute in Batavia (Java), and his staff, for friendly coöperation in this study.

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THE RESPONSE OF BLOOD DONORS TO IRON.

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ALTHOUGH occasional blood-letting is sometimes beneficial and is rarely deleterious, frequent donations inevitably cause anemia in the donor. Snapper, Liu, Chung and Yu¹⁰ observed that this anemia was of the hypochromic microcytic type and reported that it responded strikingly to iron therapy, whereas hemoglobin regeneration was uncertain in anemic donors not receiving iron.

In view of the fact that the rapidity of hemoglobin regeneration is of paramount importance to the professional donor and sometimes to the recipient as well, it is curious that the routine administration of iron to donors is not more widespread. It therefore seemed interesting to evaluate iron therapy as applied to repeated blood loss through donation. The present report gives the results of alternate administration and withdrawal of iron to a group of professional donors* during the spring and summer of 1937.

Material and Methods. Reliability in coöperation was regarded as the most important prerequisite in selecting the group for the study. Since the donors were fully aware that a satisfactory hemoglobin level was essential for donations, and that such a level was presumably best maintained by taking iron, it was often difficult to prevent unreliable donors from indulging in self-medication during the control periods. The group was further restricted to include only those men who had at least one course of iron, who gave at least two donations and whose records were followed for at least 5 weeks. There were 27 white male donors in this group. All were healthy and fairly intelligent. With the exception of three clerks and one barber, all were mechanics, laborers, or factory workers. They ranged in age from 22 to 49, averaging 34. The experiment was continued for 16 weeks, but the average time of study for the entire group was only 12 weeks.

Iron was usually administered when the hemoglobin was low and withdrawn when a satisfactory response had been obtained. The form of iron used was exsiccated ferrous sulphate in 3 gr. tablets† (corresponding roughly to 5 gr. U.S.P.). The usual dose was 4 tablets a day. The experience of the agency had shown that this form of iron was most satisfactory for blood donors because of its convenience, effectiveness and freedom from unpleasant gastro-intestinal reactions.

The routine of the agency was not altered except for the systematic administration and withdrawal of iron and the insistence on unusually frequent check-ups. Hemoglobin was read by the acid hematin method, using a standardized Hellige wedge type hemometer.

Results. The subjective response to iron was striking. Most of the donors felt better generally and had better appetite while receiving it. A gain of weight was noted in a few instances. No gastro-intestinal upset was reported.

* The Mixon Blood Donor Agency of Brooklyn, N. Y., coöperated for this study.

† Feosol supplied by Smith, Kline & French Laboratories.

Table 1 shows the variations in donations and medication.

TABLE 1.—DETAILS OF FERROUS SULPHATE DONATION.

	Range.	Average.
Number of donations per donor . . .	2-10	4
Number of weeks per donor . . .	5-16	12
Total blood given per donor . . .	500-4150 cc.	1580 cc.
Weekly average per donor . . .	45-343 cc.	132 cc.
Proportion of time on iron therapy . .	13-80%	50%

The administration of iron was regularly followed by a rise in hemoglobin. One donor had never had a hemoglobin reading of more than 12 gm. per 100 cc., but had 14 gm. per 100 cc. after the first 2 weeks of therapy. During the next 6 weeks on iron he gave a liter of blood in 3 donations, in spite of which his hemoglobin rose to 14.8 gm. In 2 cases there was little or no response to the routine dose of iron, but there was a satisfactory rise of hemoglobin when it was increased to 2 3-gr. tablets t.i.d. There was regularly a depression of hemoglobin immediately after donations. Although this was often followed by stimulation, the return to the original level was usually prolonged if iron was not given.

The hemoglobin curves of 4 typical cases are given in Chart 1.

After 19 donations (500 cc.) which occurred during iron therapy, and subsequent to which iron medication was continued without additional donations, hemoglobin returned to the previous level in an average of 11 days. In 7 similar donations occurring shortly before or after the withdrawal of iron, regeneration was also satisfactory. However, in 5 such donations not immediately preceded or followed by iron therapy, regeneration was much slower. In 2 of these latter cases, the hemoglobin returned to the previous level in 17 and 19 days respectively, but in the other 3 it was still 1.6 to 3 gm. per 100 cc. below the previous level 2 to 4 weeks later, at which time iron was given.

The per cent per day hemoglobin change is shown in Chart 2. This was determined by dividing the percentage hemoglobin change (15.6 gm. = 100%) by the number of days. The calculation was based on all periods where there were hemoglobin readings at intervals of approximately 1 week and where there were no donations or any change of regimen. The range was from +0.2% to +1.3% per day (with an average of 0.67%) during iron therapy, and from -1.7% to +1.6% (averaging +0.08%) without iron. The figure of +1.6% is from the chart of a donor whose hemoglobin level rose immediately after iron was withdrawn, which might indicate delayed response. The average data show that hemoglobin was regenerated 8 times as quickly when the donors were receiving iron.

Physical characteristics of the donors seemed to have little or no effect on the hemoglobin response to iron.

Mean corpuscular hemoglobin and reticulocyte counts tended to

rise and fall with the hemoglobin curves. The increase of reticulocytes was never marked, even after donations or during iron therapy. At such times the average was only about 2%, and in no case did the count exceed 3%.

There was little variation in white blood counts.

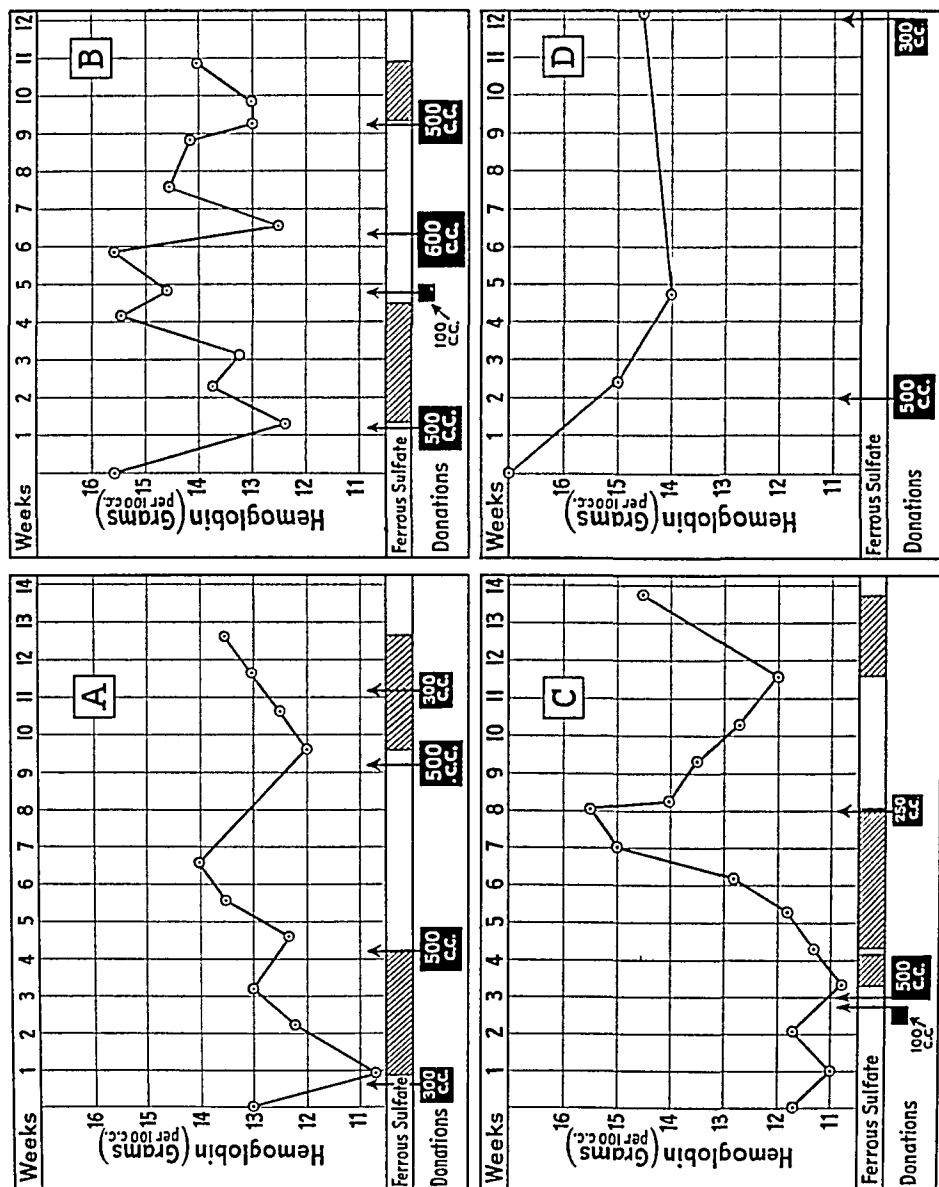
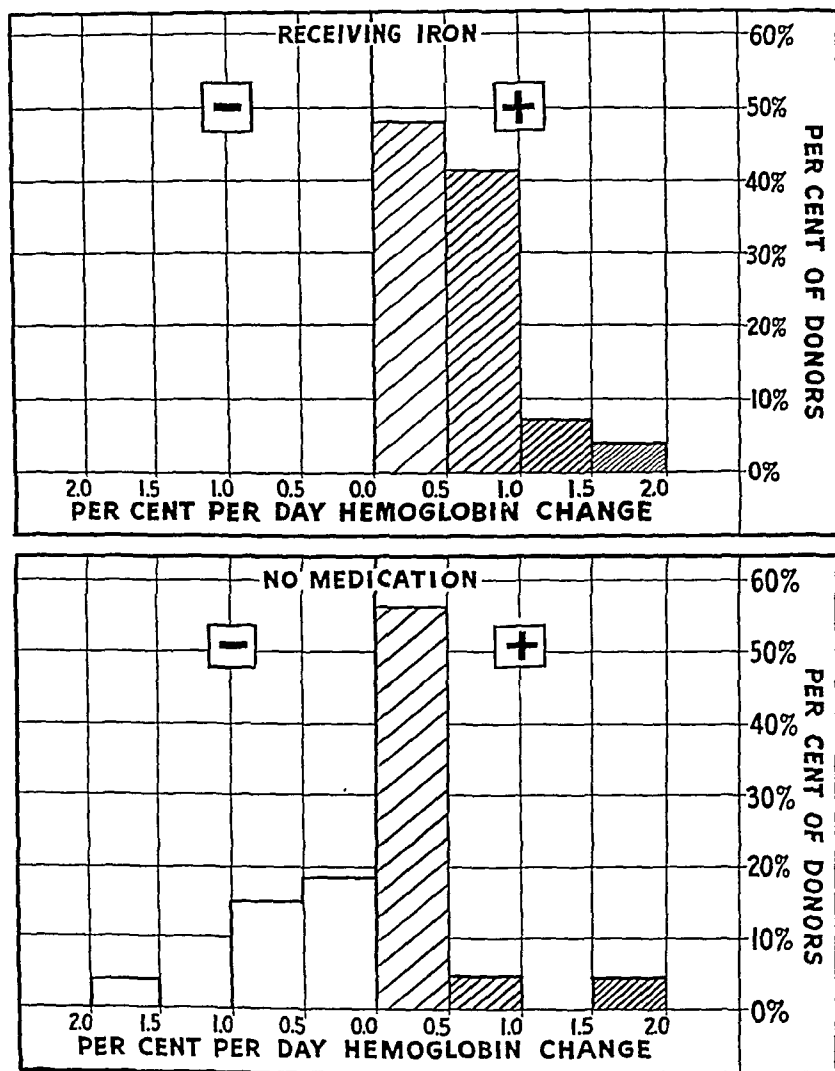


CHART 1.—HEMOGLOBIN CURVES OF 4 TYPICAL CASES.

A-B, Cases showing hemoglobin response during iron therapy and continuing after withdrawal. The protracted effect could be ascribed to hematopoietic stimulation from donations as well as to reserves of tissue iron. C, Case showing hemoglobin response to iron, but ceasing when it was withdrawn. D, Case showing the slower hemoglobin regeneration without iron medication.

It was of interest to compare the total amount of hemoglobin in the circulating blood with and without iron. The hemoglobin change (in grams per 100 cc.) during the entire periods was multiplied by blood volume in cc. according to Gibson and Evans' table² and divided by 100. To this was added the amount of hemoglobin

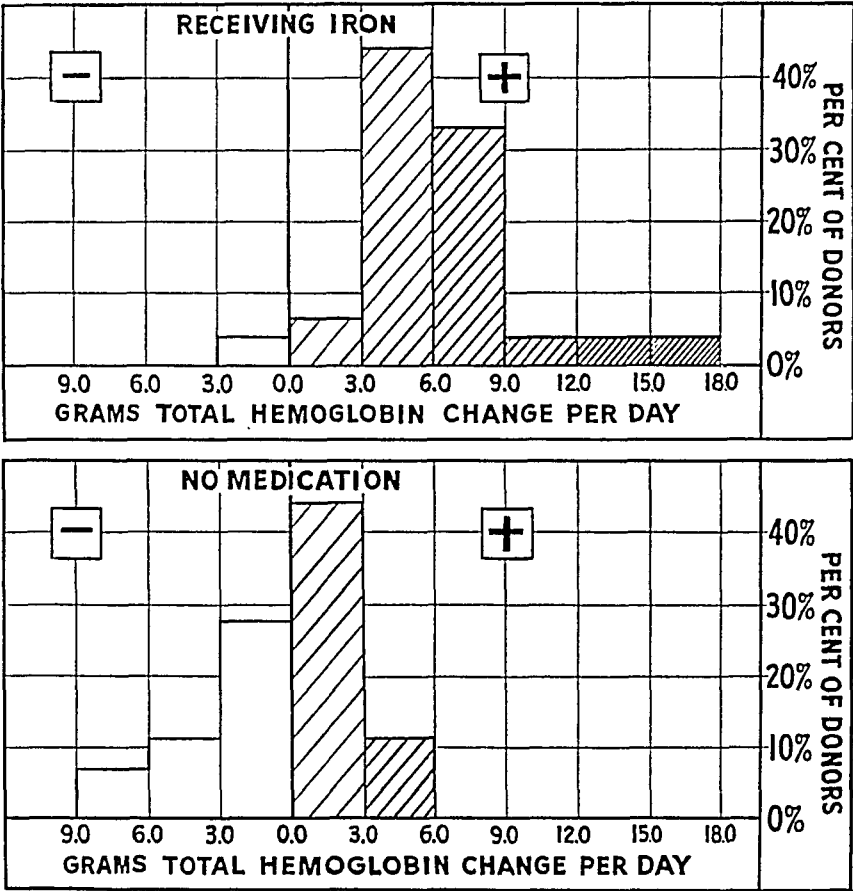
CHART 2.—PER CENT PER DAY HEMOGLOBIN CHANGE IN 27 DONORS IN PERIODS DURING WHICH NO DONATIONS OCCURRED.



in donations (found by multiplying the number of cubic centimeters of blood given by the previous hemoglobin reading and dividing by 100). The sum of these was divided by the number of days in the periods, giving the average daily rise or fall in the total amount of hemoglobin in the entire circulation. Although these calculations are based on figures which are necessarily subject to considerable

error, the difference between the negative balance found when iron was not given and the markedly positive balance in the periods of iron medication is sufficiently striking to be significant (Chart 3). The range of variation was from -1.66 to +13.8 gm. per day (with an average of 5.8) during iron therapy, and from -8.25 to +4.77 gm. per day (averaging -0.16) in periods without medica-

CHART 3.—TOTAL HEMOGLOBIN CHANGE PER DAY IN 27 DONORS.



This value was found by the formula:

$$\text{Hb. change in gm. per 100 cc.} \times \frac{\text{blood vol.}}{100} \times \frac{\text{donations in cc.} \times \text{Hb. in gm. per 100 cc.}}{100} \div \text{Number of days}$$

tion. There was only one negative figure during medication. This was observed in a donor showing an initial rise of 1.5 gm. hemoglobin per 100 cc. in the first 2 weeks of iron therapy but a drop of 2.5 gm. per 100 cc. in the next 3, during which period 2 donations were given. Following withdrawal of iron, the hemoglobin increased 4 gm. per 100 cc. in 2 weeks, which seemed attributable to delayed response to iron, hematopoietic stimulation from the dona-

tions, or to both. Similar effects could be suspected in most of the other cases where there was a positive hemoglobin balance during periods without iron.

A study was also made of the hemoglobin balance of 3 donors who had original readings of over 16 gm. per 100 cc. and who were not given iron. One showed a loss of 0.3 gm. total hemoglobin per day over a period of more than 2 months, and the others gained 0.7 and 1.3 gm. per day respectively. The larger of these gains would be sufficient for a donation of 132 cc. once every 17 days, as opposed to the average donation of 132 cc. every week as given by the 27 subjects shown in Table 1, and it would allow for a 500 cc. donation only once in 63 days, as compared to the 11-day period which sufficed for the 19 subjects receiving iron, as stated above.

Comment. In interpreting the results, the complexity of hemoglobin regeneration must be borne in mind. The immediate *apparent* regeneration is probably due to utilization of body stores, as suggested by Hutchison.⁵ But this mobilization cannot effect permanent regeneration unless the deficiency is compensated by iron intake.

The hemoglobin regeneration represented in Chart 2 (0.67% per day) is not phenomenal compared to the response that may be expected in severe iron-deficiency anemia. But as Heath⁴ states, the results obtained are in inverse proportion to the degree of anemia; and in this series of cases, most of the subjects could not properly be classed as anemic at all. The amount of blood that can be safely withdrawn varies, of course, with the individual. Merklen, Israel and Apffel⁹ felt that 100 cc. per month should be the usual limit. This figure agrees with the limit set by Giffin and Haines,³ but Brewer¹ and Martin and Myers⁸ were more conservative. Jones, Widing and Nelson,⁶ on the other hand, found no ill-effects from donations of 400 cc. repeated 4 or 5 times at 4- to 5-day intervals.

Since donors receiving iron gained an average of 5.77 gm. of total hemoglobin per day, they could be expected to give 500 cc. at intervals averaging 2 weeks without lowering the hemoglobin level. The negative hemoglobin balance of subjects without benefit of iron (Chart 3) indicates that much longer periods of regeneration are necessary when no medication is given. Although infrequent blood-letting may be beneficial, repeated hemorrhage leads inevitably to a state of anemia unless remedial measures are taken. In view of the fact that the hemoglobin usually continued to rise for some time after iron was withdrawn, the best time to give iron is apparently before rather than after blood loss, in order to supply sufficient stored iron to compensate for the expected fall of the hemoglobin level. When there is frequent repetition of blood loss, or when response to iron is less than average, medication should, of course, be protracted.

As regards the amount of blood loss as well as its periodicity, menstruation is comparable to professional donation. Women who lose but little blood can make up the iron deficiency through ordinary nutrition. But according to Leverton and Roberts'⁷ figures, the average iron requirement for menstrual loss is 15 mg. a day, which is more than is found in the average diet. Supplementary iron therapy is therefore indicated for the average menstruating woman as well as for the average regular blood donor.

Summary. The hemoglobin response of 27 active professional blood donors was studied under iron therapy and without medication.

It was found that hemoglobin regeneration after donations took place 8 times more rapidly when iron was given.

The return to the previous level was complete in an average of 11 days after a 500 cc. donation under iron therapy, whereas a far longer period was necessary when iron was withheld.

A rough calculation of the amount of hemoglobin in the total circulation revealed the fact that the average active donor in this series could not maintain a positive balance without iron medication.

It was found that the response to iron usually continued after its withdrawal, indicating that the most effective time to administer iron is before blood loss.

It is concluded that the diet of regular donors should be supplemented with iron. Ferrous sulphate, because of its convenience and freedom from reactions, was regarded as a very satisfactory form of iron for blood donors.

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BEE VENOM IN THE TREATMENT OF CHRONIC ARTHRITIS.

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BEE stings have been used in the treatment of arthritis for nearly a century. The idea began with an empirical observation that some victims of arthritis were relieved of their pain after accidental encounters with bees, and that bee keepers seldom suffered from rheumatism. Phillip Terc¹⁰ and later other European physicians deliberately exposed patients to stings of the honeybee with reportedly good results (Beck¹). The idea has become so popular in this country that a bee keeper remarked to the writer that selling

bee stings to rheumatics yielded a better income than the sale of the honey.

Chemically, bee venom is an albumin-free sapotoxin allied to snake venom combined with a poison similar to cantharides (Hench, *et al.*⁵). It contains some histamine, but no formic acid. The therapeutic action depends on a foreign protein reaction (Kroner⁶), a counter-irritation, or a histamine-producing action (Beck¹).

The assumption that arthritis results from impaired circulation of blood and lymph in the joint tissues leading to accumulation of lactic acid and permitting bacterial growth, forms the basis of the rationale of this treatment (Beck). Bee venom has a vasodilating action thus increasing local blood supply and tending to correct the basic fault.

Several forms of bee venom for injection have been produced to facilitate the regulation of the dosage, and eliminate the obvious objections to direct bee stings. Apicosan, Apicur, Ven-apix, and Lyovac Bee Venom are examples of bee venom solutions.

Many European investigators have employed bee venom in the treatment of chronic arthritis and report good results (Sauerwald,⁹ Thompson¹¹). American reports are fewer and a little less optimistic. Kroner and his co-workers⁶ treated a series of 100 cases of atrophic arthritis, but used no controls. These investigators reported no cures, but 35 patients were markedly improved, 38 were moderately improved, or, in all, 73 patients were improved by the treatment. Relief from pain was reported to be definite and lasting, and a decreased erythrocyte sedimentation rate was noted. In a later paper one of the co-authors (Nicholls⁷) reported discouraging results in 27 patients treated with actual bee stings.

Burt² analyzed the results in 50 of his series of 200 cases in which bee venom in solution was employed. Sixteen were "much better," 9 were "better," 15 were unchanged, and 10 patients were worse after the treatment. He concluded that bee venom therapy is by no means specific but of definite value in some cases. Other reports, such as those of Douthwaite⁴ and Reichart,⁸ are more skeptical of the virtues of bee venom in the therapy of arthritis.

The present study was undertaken to evaluate the benefit from bee venom in solution in the treatment of arthritis in a controlled series of cases. Fifty-nine patients suffering from rheumatic diseases, 38 of whom were female and 21 were male, were taken at random from the arthritis clinic and wards of the Pennsylvania Hospital. The age of the patients ranged from 23 to 69 years, and the duration of the disease from 5 months to 33 years. All the patients were examined and obvious foci of infection eliminated before treatment was begun. The prescribed diet was low in carbohydrate, high in vitamins, and of adequate caloric value for each patient. No treatment except the injections of bee venom in solution was given during the period of observation.

Since the psychic benefit from any vigorous form of therapy in chronic illness was appreciated, 17 patients were included in a control group. In this group there were 9 cases of atrophic arthritis, 7 of hypertrophic arthritis, and one of mixed arthritis. These patients were given injections of a mild non-specific protein solution.

Forty-two patients were treated with bee venom in solution. Twenty-four of these had atrophic arthritis, 10 had hypertrophic arthritis, and 6 had the mixed form. One case of rheumatoid spondylitis, and one of severe chronic fibrositis were included.

Determinations of erythrocyte sedimentation time and Schilling differential leukocyte counts were routinely carried out before and after the course of treatment on all patients. These two tests help to indicate the activity of the rheumatic disease.

Method. Two brands of bee venom solution were used in the study. Ven-apis, a solution of bee venom, was supplied in 3 concentrations to facilitate increasing dosage. "Lyovac" Bee Venom, a powdered form, was supplied with ampoules of normal saline so that injections could be given immediately after dissolving the venom to prevent inactivation. Ven-apis was used in the first 22 cases, and the "Lyovac" Bee Venom in the last 20. Since results from the two preparations were closely parallel, no distinction will be made between the groups.

Injections were given usually over the extensor surface of the most painful joints. The skin was prepared with acetone, as alcohol inactivates the venom. A small initial test dose was injected to detect the degree of sensitivity. The venom solution was given in intracutaneous wheals containing 0.1 cc. each, and spaced 1 to 2 cm. apart.

The number of wheals was increased twice a week until the patient received the equivalent of 10 to 30 bee stings per visit. The amount given was determined by the individual reaction to the solution.

Only patients treated more than 6 times were included in the series. Most of the patients were injected 20 times or more, or received the equivalent of more than 100 bee stings.

Each of the patients in the control group was given 15 injections of Proteolac, a milk protein solution, intramuscularly or intravenously, at weekly intervals.

Results. Of the 42 patients with chronic arthritis treated with bee venom solution none was completely relieved of his disease. Three patients were markedly improved, 5 more were moderately but perceptibly better, and 9 experienced some relief during the course of treatment but relapsed soon after the injections were discontinued. Twenty-two patients were unaffected by bee venom therapy, and 3 were definitely worse after treatment.

In the control* cases treated with Proteolac, 3 were perceptibly improved, 5 more were better while receiving injections but they obtained no lasting benefit; and the condition of the remaining 9

* The word "control" must here be accepted with reservations, as "control" would, strictly speaking, require the use of a therapeutically inert material, not one that produces non-specific protein shock. It must be kept in mind that non-specific protein reaction may at times be helpful in arthritis and that the effect of bee sting itself may be in part on such a non-specific protein reaction basis.—EDITORS.

patients was unchanged. No untoward reactions occurred in these cases.

Decreased pain and stiffness in the joints, increased appetite and increased strength were subjective signs of improvement. Objectively, the criteria were: decreased swelling and increased mobility of the joints involved, gain in weight, increased hemoglobin and red blood cells, a decreased number of immature neutrophils in the blood count, and a decreased erythrocyte sedimentation rate.

The length of treatment and actual number of injections did not have a direct effect on the degree of improvement. In the patients showing lasting benefit from bee venom treatment the average number of visits was 18, with improvement showing itself as early as the third week.

In the unimproved group, the average number of treatments was 21, with one patient experiencing no change after 32 injections. The patients made worse by the treatments had 8, 9, and 17 injections respectively.

In the 8 patients improved following bee venom therapy the decrease in the corrected erythrocyte sedimentation rate did not closely parallel the actual degree of improvement felt by the patient, but in 6 a decrease of more than 6 mm. was found. The filamented-non-filamented neutrophil ratio did not closely follow the degree of apparent benefit from treatment, but shifts toward normal were noted in 7 instances. A few of the unimproved patients showed improvement in sedimentation rate, but the change was always only a few millimeters.

TABLE 1.—RESULTS IN 42 CASES OF ARTHRITIS TREATED WITH BEE VENOM.

Type of arthritis.	No. of cases.	Greatly im- proved.	Moder- ately im- proved.	Temp. im- proved.	Un- changed.	Worse.
Atrophic (rheumatoid):						
Advanced	15	1	2	1	9	2
Early	9	1	1	1	5	1
Mixed: advanced	6	0	0	3	3	0
Hypertrophic	10	0	2	4	4	0
Fibrositis	1	1	0	0	0	0
Rheumatoid spondylitis	1	0	0	0	1	0

In Table 1 the 42 cases are subdivided into types of arthritis with results by sub-groups. Table 2 shows results in the control series for comparison.

TABLE 2.—RESULTS IN 17 CASES OF ARTHRITIS TREATED WITH PROTEOLAC.

Type of arthritis.	No. of cases.	Greatly im- proved.	Moder- ately im- proved.	Temp. im- proved.	Un- changed.	Worse.
Atrophic (rheumatoid):						
Advanced	6	0	1	1	4	0
Early	3	0	1	0	2	0
Mixed	1	0	0	1	0	0
Hypertrophic	7	0	1	3	3	0

Untoward reactions to the injections of bee venom solution were fairly uncommon. In several instances the local reaction was excessive, the wheals showing pseudopod formation, and edema of the area ensued. Little generalized reaction occurred except for mild headache which was occasionally complained of. Symptoms of toxicity developed in 2 patients, necessitating termination of treatment. Both patients had headache, weakness, irritability, and frequency of urination, and definite albuminuria was noted in one.

Discussion. The most marked improvement following bee venom therapy was seen in the case of fibrositis, in which an almost complete remission of symptoms occurred. Reichart⁵ and other workers have found that fibrositis is more responsive to bee venom therapy than rheumatoid arthritis. The frequent spontaneous remissions characteristic of chronic fibrositis³ must be borne in mind in evaluating results, however.

One case of advanced atrophic arthritis showed a definite symptomatic and objective improvement. This woman had been very much discouraged with results from other forms of treatment, but improved definitely with the use of bee venom. Pain, swelling, and stiffness of the diseased joints was decreased, her general health became better, and the blood count and sedimentation rate improved. The good result in the early case of rheumatoid arthritis must be at least partially credited to the removal of diseased tonsils 6 weeks before treatment began.

The course of chronic arthritis is rarely uniform. The victims suffer a series of relapses and partial remissions, perhaps even more disheartening than a steady downward course. The variation in intensity of the arthritis occurs independent of treatment, and makes evaluation of improvement secured from any one form of therapy very difficult. Temporary improvement and subjective benefit should not be regarded with much optimism.

The proportion of patients showing subjective or temporary improvement was about the same in the subdivisions of the treated group, as well as in the control group. This improvement could be attributed to psychic benefit alone.

The most interesting, and perhaps most significant, case was that of J. R. For 23 years this man had suffered from rheumatoid arthritis, and his principal occupation for the past 18 years was keeping bees! He had been stung hundreds of times and he had "sold" bee stings to other arthritics, but still had the complaints and deformities characteristic of advanced atrophic arthritis. This patient was given a course of bee venom injections with no improvement at all. It must be stated, however, that he was actually immune to bee stings, there being no local or general reaction following large doses of venom.

Summary. 1. Forty-two patients with chronic arthritis were treated with an injectable solution of bee venom. Eight patients were improved. Of these, 2 cases of rheumatoid arthritis and one of fibrositis were markedly better.

2. The number of treatments varied from 6 to 32 over periods ranging from 4 weeks to a year. The length of treatment and total dosage showed no apparent correlation with degree of improvement.

3. Seventeen patients were given foreign protein injections, and were regarded as a control group. Three of these patients showed lasting improvement.

4. The incidence and degree of improvement were very discouraging, and all but one of the patients, the one suffering from fibrositis, are still seeking relief from their disease. Even though a few patients showed definite and lasting improvement, it is felt that a painful, tedious, expensive, and somewhat toxic form of therapy should yield much better results to justify its continued use.

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HEBERDEN'S NODES.*

HEREDITY IN HYPERTROPHIC ARTHRITIS OF THE FINGER JOINTS.

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THE term Heberden's nodes today indicates enlargements of the terminal joints of the fingers due to hypertrophic arthritis, though Heberden himself spoke of hard knobs "particularly a little below the top near the joint." They arouse the patient's interest by the unsightly deformity which results rather than from any severe degree of discomfort or disability which they produce. Alarm is also occasioned because of the fear that they betoken a crippling disease. Such apprehensions are without foundation because, although Heberden's nodes are properly regarded as a manifestation of hypertrophic arthritis, the disease is most often limited to the

* Read at the annual meeting of the American Rheumatism Association in New York City, June 10, 1940.

fingers. Many generalizations concerning hypertrophic arthritis are applicable to Heberden's nodes but certain advantages are to be derived from considering this disease as a distinct clinical entity. The purpose of this paper is to present evidence that the occurrence of Heberden's nodes is strongly influenced by heredity.

Despite the benign nature of the disease Heberden's nodes are frequently mentioned in the literature. Their familial nature has been pointed out. Charcot¹ stated, "It is a hereditary disease and may appear in several members of the same family." Duckworth² describes a family in which Heberden's nodes occurred in four generations in direct descent affecting mostly the female line but involving 3 brothers and 1 sister of one generation. Wick³ discovered familial involvement in 6 cases of 100 studied. Monroe³ states that, "Hereditary influences may be at work in those in whom they appear early in life. Such a familial trait has been reported by the several patients under thirty years of age that I have had."

Heberden's nodes may occur as a result of direct trauma, usually a single episode, severe enough to be distinctly recalled as to time and circumstance. The injury is followed promptly by enlargement which remains constant after several months. These so-called traumatic nodes are common in men and are most often confined to one finger or at least to one hand. Traumatic nodes, when they occurred, have been eliminated from this study because our attention is confined to another form of the disease, idiopathic Heberden's nodes. These arise spontaneously without relation to trauma, starting in one finger but spreading, in a period of several months to several years, to other fingers until all may be affected. A previous study⁴ based on observation of nearly 7000 individuals showed that the incidence of both traumatic and idiopathic Heberden's nodes varies with race, sex and age differences. Figure 1 shows the incidence of idiopathic nodes in white people classified according to sex and age by decade. The number of persons examined in each group is indicated. As will be seen, the incidence of idiopathic nodes is low until the age of 60, after which it rises rapidly to nearly 30% in the ninth decade.

The present study concerns 68 families of white people with Heberden's nodes—66 of whom are women and 2 are men. A complete family history was obtained from each informant or index case, including names, ages and condition of the fingers of parents, brothers and sisters. Brothers and sisters dead before the age of 20 have been eliminated from all the following tabulations. An attempt was made to examine as many female relatives as possible. A control series of patients in City Hospital was studied for comparison. Index cases for this were women selected only if they had no arthritis of any kind and if they had sisters available for examination. Information concerning 442 individuals is included in the study series and 195 in the control series.

Of 67 mothers of affected women, 21 were said to have Heberden's nodes. These figures are based almost entirely upon history, as only 4 of these mothers were available for examination. Women with Heberden's nodes are conscious of their deformity, are disturbed at the appearance of their fingers and become observant of the condition in other people, particularly in relatives. The history of the occurrence of Heberden's nodes in this series is probably reliable. The history of absence of nodes is not so reliable, because many of the affected individuals had not seen their mothers for years prior to death and therefore had no definite knowledge concerning the condition of their mother's fingers. It seems likely that the number of affected mothers as given, if it be in error at all, is low rather than high.

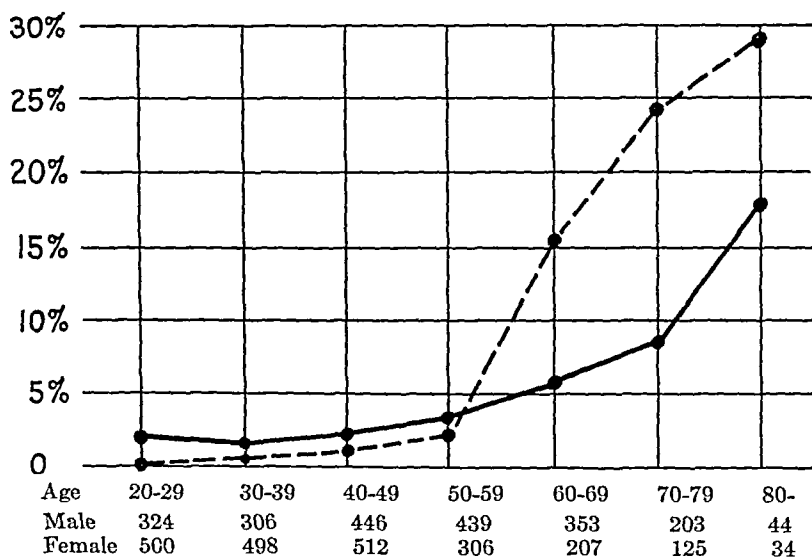


FIG. 1.—Percentage incidence of idiopathic Heberden's nodes in white people according to age. Solid line, males; broken line, females. Figures at bottom indicate number of individuals examined in each group to determine incidence.

Of 129 sisters of affected women, 33 were said to have Heberden's nodes. Of the 33 affected women the diagnosis was confirmed by examination in 17 instances, and by response to questionnaires in 5 instances. The diagnosis was confirmed in 66% of the cases. Of 96 unaffected sisters, 20 were examined personally and 7 responded to questionnaires. The absence of Heberden's nodes was confirmed in only 28% of the cases. It seems likely that the number of affected sisters of affected women, if it be in error at all, is low rather than high.

In the control series, of 43 mothers of unaffected women, none were reported to have had lumps, knobs or enlargement of the finger joints. This is of little importance except to indicate that women without finger enlargement are not observant of the condi-

tion. Of 109 sisters of unaffected women, 5 were found to have Heberden's nodes. Four were examined and 1, a deceased sister, was accepted on the basis of history. Of the 104 unaffected sisters, 77 (74%) were examined personally. Eighteen were dead and 9 were not contacted. Of the 27 cases not contacted, 18 were below the age 50 when Heberden's nodes are rare. Any error in the series of sisters of unaffected women seems likely to be small.

TABLE 1.—OCCURRENCE OF HEBERDEN'S NODES IN RELATIVES OF AFFECTED PERSONS—68 FAMILIES.

Age groups.	Age incidence.	In 67 mothers.			In 129 sisters.		
		Total mothers.	Expected affected.	Recorded affected.	Total sisters.	Expected affected.	Recorded affected.
20-29 . . .	0.000	2	0.000	0	6	0.000	0
30-39 . . .	0.004	4	0.016	0	16	0.064	1
40-49 . . .	0.010	3	0.030	0	17	0.170	3
50-59 . . .	0.026	9	0.234	0	39	1.014	10
60-69 . . .	0.155	19	2.945	8	31	4.805	14
70-79 . . .	0.247	16	3.952	9	11	2.717	2
80- . . .	0.294	14	3.823	4	9	2.646	3
Total	67	11.000	21	129	11.416	33

A further analysis of the mothers and of the sisters of affected women, comparing the number of affected persons actually found with the normal expectancy in a group of the same size and age distribution of the population in general is shown in Table 1. These figures are derived by multiplying the total number of subjects in each decade by the incidence for this age and totalling them. The number of sisters recorded affected in these families is lower than actual because the index cases have been omitted. The necessity for this procedure becomes obvious if we postulate a series of families with but 1 daughter. In such a series the occurrence would be by definition 100%. Among the 67 mothers 21 cases are reported, but only 11 cases are to be expected. This figure of expected affected is slightly high because the age of mothers as given in all but 4 cases is really the age of death. The incidence of the population in general is based on living persons, before they died. Despite this, mothers of affected women have Heberden's nodes nearly twice as frequently as the population in general. Among 129 sisters of affected women 33 cases are found, compared to 11.4 expected, about three times the normal. Among 109 sisters of unaffected women 5 cases are found, compared to 6.26 expected, a reasonably close approximation to normal. More detailed information concerning mothers and sisters of unaffected women is shown in Table 2.

Analysis of fathers and brothers of affected women will not be given in detail. Of 54 fathers concerning whom information is

available, only 1 was reported affected, compared to 4.57 expected. Of 124 brothers described, only 1 was said to be affected, compared to 4.99 expected. Of the 124 brothers, only 81 were alive and only 42 were living in Ohio. Considering only the 42 reported to be in Ohio but 1.91 was to be expected affected. It seems likely that a more thorough investigation of the available brothers will reveal a few unsuspected cases. Such search seems unlikely to alter our conclusions, so it has not yet been attempted.

TABLE 2.—OCCURRENCE OF HEBERDEN'S NODES IN RELATIVES OF UNAFFECTED PERSONS—43 FAMILIES.

Age groups.	Age incidence.	In 43 mothers.			In 109 sisters.		
		Total mothers.	Expected affected.	Recorded affected.	Total sisters.	Expected affected.	Recorded affected.
20-29 . . .	0.000	0	0.000	0	8	0.000	0
30-39 . . .	0.004	1	0.004	0	17	0.068	0
40-49 . . .	0.010	2	0.020	0	27	0.270	0
50-59 . . .	0.026	9	0.234	0	28	0.728	0
60-69 . . .	0.155	12	1.860	0	17	2.635	2
70-79 . . .	0.247	12	2.964	0	12	2.564	3
80- . . .	0.294	7	1.988	0	0	0.000	0
Total	43	7.070	0	109	6.265	5

Various family combinations are worthy of note. Of 68 families, mothers were affected 21 times. Three generations in direct descent through the female line were found affected in 4 families. In 2 other instances grandmothers of index cases were affected, the mothers being spared. In these families, however, the mother died before the age of 35 years. Several examples of descent through the paternal line were noted. The father himself was affected only once, but in this family the mother was affected also. In 3 families a paternal aunt was affected, the father being spared. In 19 families more than 1 sister was afflicted. In only 28 of the 68 families studied was no evidence of familial involvement discovered. In 9 of these 28 families the index case was an only daughter.

In 3 families the probability of multiple involvement among brothers and sisters was calculated. This calculation can be illustrated very simply by a penny-tossing experiment. If one penny is tossed, the chance of its landing head up is 1 in 2. If a second penny is tossed, the chance of its landing head up is also 1 in 2. If both pennies are tossed together, the chance of both resting head up is 1 in 4, the product of the individual chances. The probability of a person having Heberden's nodes is the incidence. The probability of several cases occurring in the same family by chance alone is the product of their combined incidences. The first family is

illustrated by Figure 2. Four sisters are involved, 3 of whom were seen. These women were advanced in years so that the incidence is high. The probability of 4 cases occurring at this age in 1 family

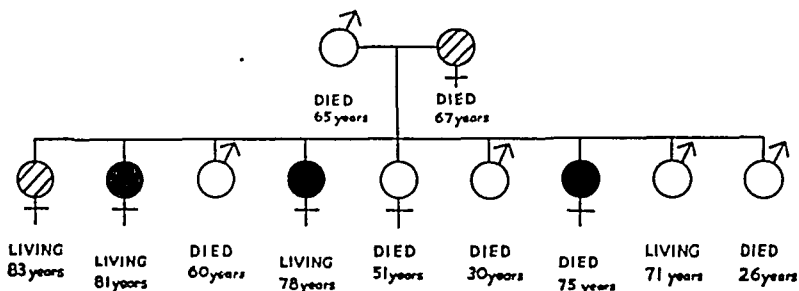


FIG. 2.—*First Family*. Black circles indicate affected individuals examined. Hatched circles affected individuals not seen. The probability for involvement of individual affected members in this family is 29.4%, 29.4%, 24.7%, 24.7%. The probability for such involvement in one family by chance alone, $0.294 \times 0.294 \times 0.247 \times 0.247 = 0.00525$. This combination might be expected to occur by chance alone once in 190 families.

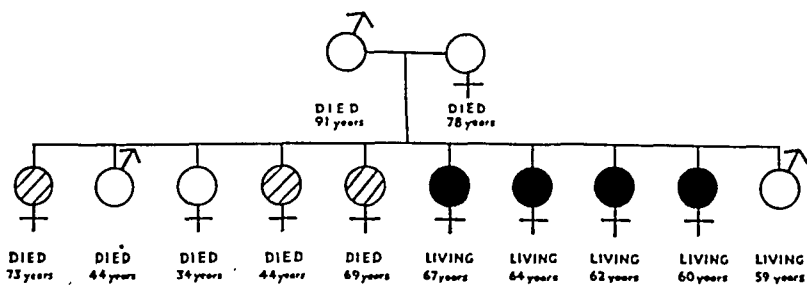


FIG. 3.—*Second Family*. The probability for individual involvement in this family is 24.7%, 1%, 15.5%, 15.5%, 15.5%, 15.5%, 15.5%. This combination can be expected to occur once in 4,500,000 families.

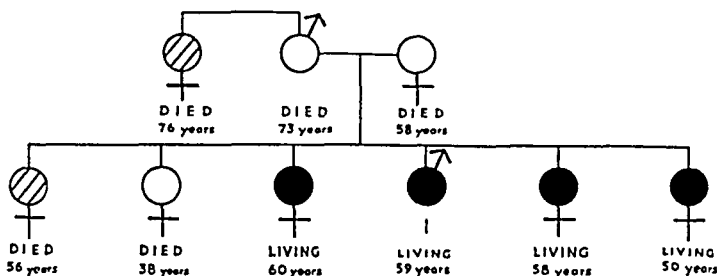


FIG. 4.—*Third Family*. The probability for individual involvement in this family is 2.6%, 15.5%, 3.6%, 2.6% and 2.6%. This combination can be expected to occur once in about 10,000,000 families.

by chance alone is 1 in 190 families. This does not seem remarkable unless we realize that this should occur once out of 190 families with at least 4 sisters who have survived until the ages of 75 to 83 years. In the second family (Fig. 3) with 7 of 8 sisters affected

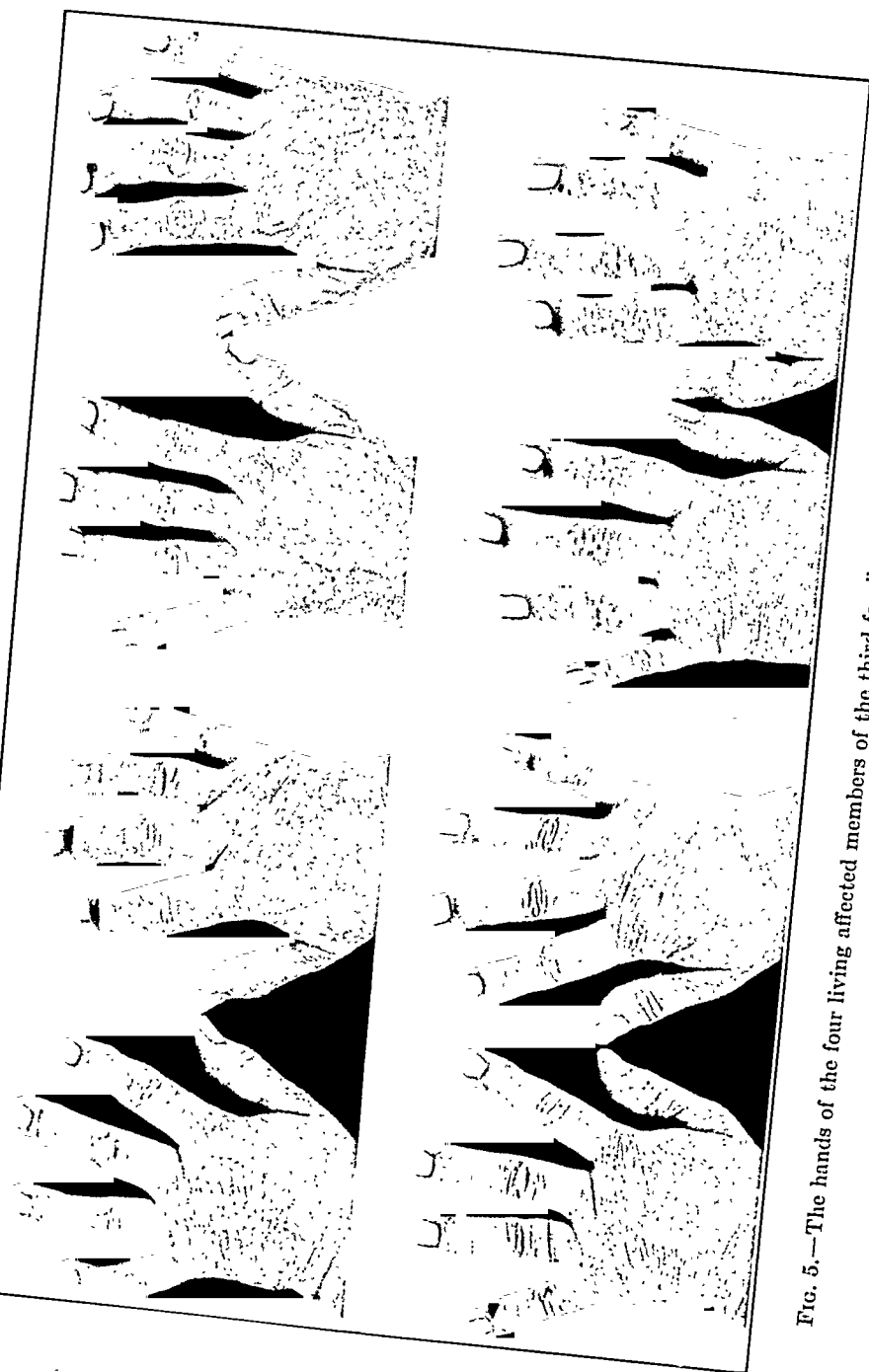


FIG. 5.—The hands of the four living affected members of the third family, showing well marked Heberden's nodes.

the probability of this combination occurring by chance alone is 1 in 4,500,000 families. Here again only 1 sister was below 50 in age. Four were in their sixties and 1 in the seventies. In the third family (Fig. 4) 4 sisters and a brother were involved. All but 1 were under 60. Here the probability is 1 in 10,000,000 families. Figure 5 shows photographs of the hands of these people. Whether we take these figures literally or not, the conclusion is unescapable that such combinations of Heberden's nodes occurring in 1 family by chance alone should be extremely rare.

Comment. This study clearly indicates the familial nature of idiopathic Heberden's nodes which is best explained by hereditary factors. The influence of common environment is eliminated because the condition occurs only in middle or later life, years after women have left the parental roof to establish their own homes and after sisters have long ceased to live together. It seems most unlikely that a common environment for the first 20 years of life might produce effects which do not become apparent for 20, 30 or 40 more years. Some type of inheritance among women is apparent but this influence in men is not so clear. The condition is relatively rare in men but it does occur. Simple dominance alone is suggested in women by the direct descent through the female line for two or three generations.

The material at hand must be analyzed by a geneticist before the exact mechanism of inheritance can be revealed. The study so far has been limited to assembling observations pertinent to the question of familial incidence. The investigation has been facilitated by certain characteristics of the disease. The deformity is so typical that the layman's opinion about its presence is reasonably reliable. The disease once present leaves a permanent record of its occurrence, and the diagnosis can be made by inspection without recourse to extensive examination or complicated technical procedures. Therefore, it was practical to determine with accuracy the incidence in the population in general. Other characteristics, however, complicate the study. The age of onset is high and many subjects free of the disease die in middle life, leaving us uncertain as to their susceptibility. Since it is a disease of later life, parents, uncles and aunts are most often not available for examination and many children are not old enough to have developed Heberden's nodes.

It may not be accurate to ascribe directly to other forms of hypertrophic arthritis all of the incidence characteristics of Heberden's nodes so far described. Definite information concerning the incidence characteristics of other forms of arthritis, showing similarities or differences between those of other arthritis and Heberden's nodes, must be observed to make these characteristics applicable. It is hoped that such similarities or differences may be apparent and

valuable conclusions drawn by analogies without the necessity of undertaking such extensive and laborious investigations as have seemed desirable in this and the previous study.

The demonstration of the influences of race, sex, age and of hereditary factors does not conclude the study of etiology in Heberden's nodes. It seems reasonable to suppose that other agencies are influential. These may operate by accelerating or retarding those organic changes necessary for the production of Heberden's nodes and thus materially affect the age of onset, or they may protect the fingers completely against the disease. The latter effect has already been observed to result from impairment of nerve function and is being studied for a report. Such other agencies influencing the onset and course of the disease, be they environmental, nutritional, circulatory, thermal, endocrinal or toxic, are not now recognizable. There is every reason to believe that, with sufficient attention, they may become so.

Conclusions. 1. Heberden's nodes or hypertrophic arthritis of the finger joints may be regarded as a distinct clinical entity. Two types are recognized and distinguishable, one arising as a result of trauma, the other arising spontaneously or idiopathically.

2. The occurrence of this disease has been shown to be profoundly influenced by race, sex, and age differences. A previous study has revealed accurately the incidences of these various classifications.

3. A study of 68 families of patients with idiopathic Heberden's nodes shows that the mothers of such subjects are affected twice as frequently and the sisters three times as frequently as the population in general. These figures, if in error at all, are more likely to be low rather than high. A control series of 43 families selected and studied in the same way showed the sisters of unaffected women to have Heberden's nodes as frequently as the population in general.

4. The occurrence of multiple cases in the same family cannot be accounted for on the basis of chance alone.

5. Hereditary factors seem best to explain the recorded observations, although the exact mechanism of transmission has not been determined.

6. The conclusions concerning Heberden's nodes are not directly applicable to other forms of hypertrophic arthritis at the present time.

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SEASONAL VARIATION IN THE WATER CONTENT OF THE RESPIRATORY TRACT OF BIRDS AND MAMMALS.

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We have reported¹ that in albino rats the water content of the tissues of the respiratory tract varies with season. During a cold spell of weather in early autumn, an increase in water was noted and during January, February and March the tissues of the respiratory tract became considerably more dry. These seasonal variations were most pronounced in the trachea but also affected slices of lung consisting chiefly of alveolar tissue ("distal" slices) or containing a large percentage of bronchial tissue ("proximal" slices). A statistical treatment of the data indicated that the differences reported were significant ones. Seasonal variations in the water content were suggested as indicative of seasonal variations in the physiology of the respiratory tract. The albino rats used in these studies were housed in a building which in the winter months was artificially heated but not air-conditioned and it was suggested that the results might have an etiologic significance in connection with seasonal variations in respiratory tract infection in man.

To this latter suggestion might be raised the objection that the seasonal changes which were reported were those of one species only and might represent a peculiarity of that species. We have therefore extended this study to include a species from another class of the vertebrate subphylum, the common pigeon. We purposely selected a bird because we reasoned that if the same seasonal variation were encountered in a bird as in the albino rat, we would be more justified in concluding that a similar seasonal variation might also occur in man. In other words, there is less biologic difference between the albino rat and man than between the albino rat and the pigeon; if a seasonal variation in the water content of the respiratory tract were found common to albino rats and pigeons, it would seem likely that it would also be common to man.

One hundred and seventy common pigeons, *Columba livia*, were used in this seasonal study which extended from June, 1939, to September, 1940. A similar number of albino rats were run at the same time to confirm the results of the previous winter.¹ To substantiate the results in the pigeons, tests were made from time to time on a total of some 90 white leghorn cockerels.

Pigeons. At approximately monthly intervals, 10 pigeons were killed without anesthesia by quickly wringing their necks. The

body cavity was opened, the trachea freed as high up as possible and the lungs quickly dissected away from the dorsal wall. As in our previous work on albino rats,¹ the removed parts were divided into three sections: first, the trachea; second, slices of the distal half of each lung taken centrifugally from the hilus; and third, the proximal half of each lung next the hilus. This division of the lung parenchyma had been made in rats because one section contained chiefly alveolar tissue while the other contained a good deal of bronchial tissue. For purposes of uniformity the same sections were made in pigeons. In pigeons, however, one section did not contain chiefly alveolar tissue and the other a preponderance of bronchial tissue as in the rat because the lung of a pigeon differs anatomically from that of the rat. In birds, air passes directly to air sacs at the periphery of the lung through the two mesobronchi and their branches the entobronchi, and respiratory exchange occurs chiefly during expiration as air is forced back from the periphery through the parabronchi and parabronchial air capillaries into the mesobronchi again and thence out through the trachea.² We have noted a uniformity of appearance, consistency and water content in all parts of the lung of pigeons, in contrast to the rat where significantly different sections may be isolated,¹ and the diagram presented by Graham² indicates that bronchial and alveolar tissues are distributed approximately evenly throughout the pigeon lung. The only advantage we gained in dividing the pigeon lung into distal and proximal sections was therefore the obtaining of duplicate water estimates on lung parenchyma, duplicates which agreed remarkably well as may be seen in Chart 1.

As the three sections were removed from each pigeon, they were separately placed in cleaned, dried and weighed weighing bottles and the wet weight estimated to the nearest 0.1 mg. Ground glass stoppers were then lightly inserted and the sections were dried at 90° C. for 100 hours in a drying oven. After cooling, they were reweighed and from the differences in weight the water content was calculated in gm. per 100 gm. of original tissue (per cent water). All of the dissection and weighing manipulations were done as quickly as possible to minimize loss of water. Since the room in which these operations were carried out was dry-heated in the winter months and the relative humidity greatly reduced, we considered the possibility that more water might be evaporated from lung sections removed during the winter months and before we could determine their wet weight. To investigate this possibility, we compared the average wet weights of sections from 10 birds removed in the ordinary dry winter air with the average of sections from 10 other birds removed in the same room with the relative humidity artificially raised to the summer level by water evaporated from shallow pans. We found the average water contents practically identical under the two circumstances which indicated that our

technique was sufficiently rapid that negligible amounts of water were evaporated during dissection and before wet weights were determined.

When the water content of the respiratory system of pigeons was measured at different seasons of the year, we obtained the results shown in Chart 1. Each point on these plottings represents the

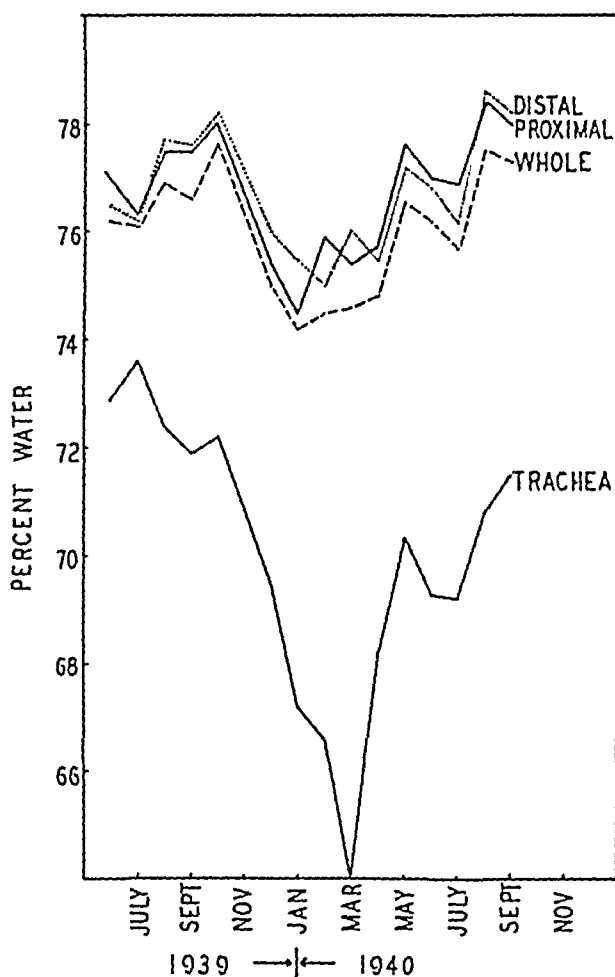


CHART 1.—Seasonal variation in the water content of the trachea, distal half and proximal half of the lungs and in the whole respiratory tract of pigeons.

mean of 10 pigeons and separate curves have been drawn for the trachea, the distal half of each lung, the proximal half of the lungs and finally the whole respiratory tract. It may be seen that there occurred a distinct fall in the water content of all sections in the winter months. The respiratory system was distinctly more dry during January, February and March. This corresponds with the results previously obtained in rats.¹ We did not notice any sharp,

distinct rise in water content in the early autumn of 1939 as we had seen in rats in October of 1938, although the mean values for lung water of pigeons were slightly higher at this season in 1939. Evidently the early autumn rise in water content does not occur as consistently as the midwinter fall. These results in pigeons therefore substantiated our previous findings in the albino rat.

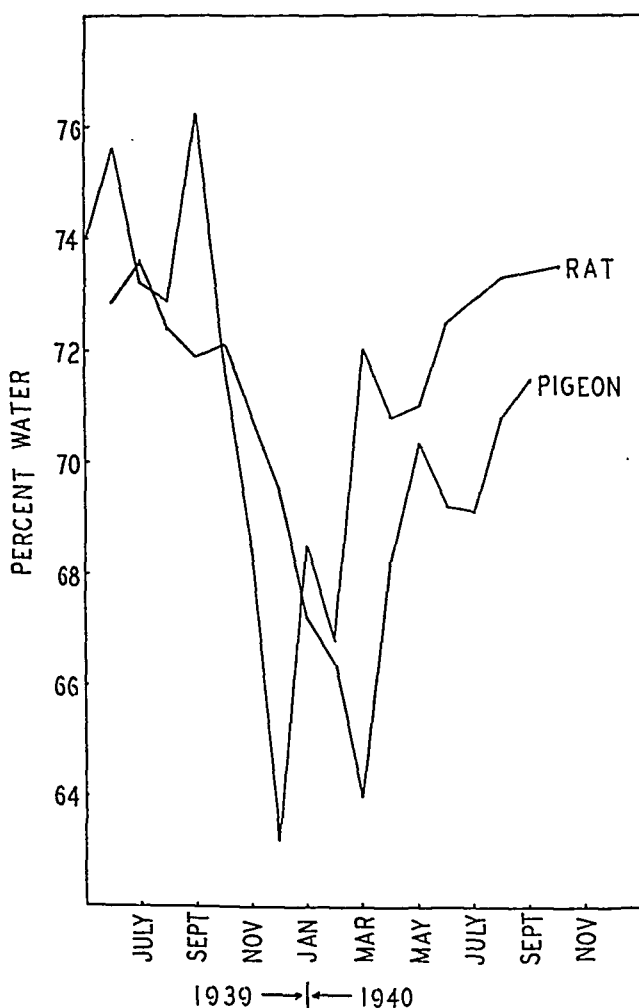


CHART 2.—A comparison of seasonal variations in the water content of the trachea of albino rats and pigeons.

Albino Rats. It was considered advisable to repeat our seasonal study on the water content of the respiratory system of albino rats, first in order to confirm our results of the season 1938-1939 and secondly to see if there was any variation from year to year. One hundred and fifty young albino rats weighing 150 to 200 gm. were used. The results in general were similar in the season 1939-1940 to the season 1938-1939. The early autumn rise in lung water was

not nearly as marked in 1939 as in 1938. The curves obtained in the albino rats during 1939-1940 were, in fact, almost identical to those obtained in the pigeon during the same year and to illustrate this similarity we have plotted the seasonal changes in tracheal water of the two species and compared these in Chart 2.

The most marked and consistent seasonal change over 2 years in one species and over 1 year in two species was the midwinter drying of the respiratory system, especially the trachea which lost up to 15% of its water in midwinter. This occurred in two biologically distinctly different species belonging to two different classes of the vertebrate subphylum. Factors common to the two species were that the results were obtained in the same locality—southeastern Ontario—and both species were housed in a building which was dry-heated in the winter months. We have as yet no experimental data to indicate whether either or both of these common factors are significant. Our present results, however, substantiate our previous¹ suggestion that similar midwinter drying of the respiratory system may occur in man and be related to respiratory infection at this time. Proof of this suggestion can be obtained only by actual measurements in man.

Cockerels. Our results of a similar seasonal study of some 90 cockerels were less consistent due, we believe, to the fact that we were unable to obtain cockerels of the same size throughout the year. We had contracted with a local poultry farm for one-pound white leghorn cockerels to be supplied each month throughout the year. We then housed these birds in our animal quarters for 1 month before killing them. Breeding and hatching had not been attempted before on this particular poultry farm in the winter months and it was found impossible to breed and hatch satisfactory chicks in the winter. We were forced to use adult hens in the winter and found that their respiratory tract was drier than that of the young cockerels. A similar drying effect of age was noted in albino rats.¹ In the following summer we compared the water content of the respiratory tract of hens with that of cockerels on the same day and used the difference as a factor to correct for the use of older birds in the winter. When this correction was made, the results were rather erratic, as might be expected, but in practically all instances the water content of the respiratory tract was lower in the winter months than during the rest of the year. We have therefore established that in three species—rats, pigeons and cockerels—there occurs a drying of the respiratory tract during the midwinter months of January, February and March, and occasionally into April.

Conclusions. We have confirmed our previous¹ observation that a distinct drying of the lungs and trachea occurs in albino rats during January, February and March in a dry-heated building in this locality (southeastern Ontario). A similar midwinter drying

of the respiratory system was further found to occur in two species of another class of the vertebrates, namely pigeons and cockerels. It seems reasonable to suggest that a similar drying may occur in man and have an etiologic significance in connection with seasonal variation in susceptibility to infection of the respiratory system.

The authors wish to thank Mr. E. R. Angehrn and the Ciba Company, Ltd., of Montreal for a grant which defrayed part of the expenses of this investigation.

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THE EFFECT OF PHENOBARBITAL ON NORMAL AND IMPAIRED DEXTROSE TOLERANCE.

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MANY investigators have studied the effect of barbiturates on carbohydrate metabolism of animals. Britton⁴ and Mulinos¹⁴ anesthetized cats with amytal and observed little or no change in the blood sugar for several hours after its administration. Page^{16a,b} working with dogs and rabbits and Cori⁵ with rats showed that amytal was without effect on carbohydrate metabolism. Atnan and Fenz¹ demonstrated no change in the blood sugar of patients with diabetes mellitus after the administration of evipal intravenously. More recently, Hrubetz and Blackberg^{12a,b} and Hrubetz, Blackberg and Dotti¹³ showed that barbiturates produced no alterations in the blood sugar of starved or normally fed rabbits during deep anesthesia; a decrease in blood sugar was noted during the recovery phase. Zerfas and McCallum²¹ and Dresbach and Randles⁷ observed no change in the blood sugar of normal fasting animals given anesthetic doses of barbiturates.

Underhill and Sprunt¹⁸ and Hines, Boyd and Leese^{10a,b} demonstrated an increase in blood sugar of rabbits and dogs anesthetized with amytal. Weiss,¹⁹ investigating the effect of soluble barbital and phenobarbital on carbohydrate metabolism in dogs and cats, found a sudden rise in blood sugar which reached a maximum in 1 to 2 hours and returned to normal within 6 to 20 hours. Bang² reported hyperglycemia in rabbits given barbital. Wierzuchowski and Gadomska²⁰ observed an increased blood sugar in dogs after

the administration of amytal. Hines, Leese and Barer¹¹ showed that dogs cannot store glycogen and have a decreased ability to assimilate dextrose after the administration of amytal. Olmsted and Giragossintz^{15a,b} studied dextrose tolerance in dogs given barbital and concluded that there was no obvious change in carbohydrate metabolism when the animals were given a meat diet exclusively. When the dogs were fed a diet containing meat and carbohydrate, a definite hyperglycemia resulted.

Ellis and Barlow⁸ noted a decrease in the blood sugar of cats and pigeons during the first 24 hours of barbital anesthesia.

Obviously, no definite conclusion can be drawn concerning the effect of barbiturates on carbohydrate metabolism. Whether the variability of results may be attributed to the different types of barbiturates used or to the lack of uniformity in the use of animal species is problematic.

Since dextrose tolerance tests are commonly performed as an aid in the diagnosis of various endocrine disorders, particularly diabetes mellitus, it seemed important to know whether barbiturates, when used in physiologic doses, would modify the normal or impaired dextrose tolerance curve. In the present study, human subjects were used and the barbiturate employed limited to phenobarbital.

Material and Methods. Thirty-seven subjects were selected from the clinics of the New York Post-Graduate Hospital. Eighteen had minor or negligible ailments and exhibited normal tolerance for sugar; 19 were either frank diabetics or prediabetics as indicated by a failure of the blood sugar to return to 120 mg. per 100 cc. or less after the ingestion of a standard amount of dextrose. All subjects were ambulatory and the diet was kept as constant as possible during the period of study. Insulin was not used by the diabetics at any time, since the glycosuria was fairly well controlled by a restricted carbohydrate intake. Sedatives had not been used prior to the test for at least several weeks, if at all. The subjects appeared in the early morning without breakfast and no smoking⁶ was permitted. Urine and venous blood specimens were obtained. Each person was then given 100 gm. of dextrose in a 50% aqueous solution by mouth. Blood and urine samples were collected at 30, 60 and 120 minutes after the ingestion of the dextrose. The chemical determinations were begun within 10 minutes after collection. Blood sugars were determined by the Folin-Wu method,⁹ urines qualitatively by a modified Nylander reagent (Galatest) and quantitatively, where indicated, by the Benedict method.³

Each of 24 subjects (13 with normal dextrose tolerance and 11 with impaired tolerance) ingested 0.066 gm. of phenobarbital 3 times a day for 7 days and on the morning of the eighth day, the dextrose tolerance was again determined under identical conditions. It is fair to assume that the phenobarbital was taken as ordered since each complained of the marked sedative effect of the drug; moreover, this was further evident objectively. It was planned to have these subjects return a third time for similar tests after discontinuing phenobarbital for 7 days, but since many objected to the frequent venipunctures, this plan was discarded. As a control series, therefore, 13 subjects (5 with normal dextrose tolerance and 8 with impaired tolerance) were given placebos (calcium carbonate, 0.3 gm., 3 times daily for 7 days) and dextrose tolerance tests carried out before and after the ingestion of the calcium carbonate.

Results. In order to conserve space, the individual blood sugar curves are not recorded. The observation appeared to be fairly consistent throughout the study, namely, that normal subjects or patients with diabetes or prediabetes frequently showed an increased tolerance for dextrose on reexamination 1 week after an initial study.

Chart 1 demonstrates that the increased tolerance for carbohydrates in normal subjects after ingesting phenobarbital is apparent and not real. The similarity in the mean curves for both the phenobarbital and placebo groups is striking. Chart 2 shows that

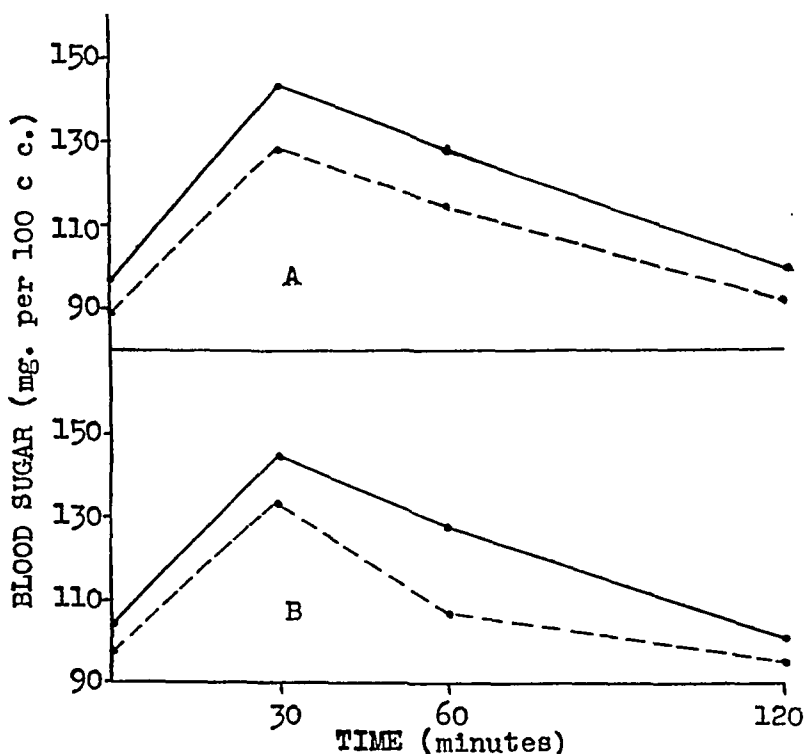


CHART 1.—A, The solid line indicates the mean dextrose tolerance curve in 13 normal subjects prior to the ingestion of phenobarbital, and the broken line the mean dextrose tolerance curve after the ingestion of 0.2 gm. of phenobarbital daily for 7 days. B, The solid line indicates the mean dextrose tolerance curve in 5 normal subjects prior to the ingestion of placebos, and the broken line the mean dextrose tolerance curve after the ingestion of 1 gm. of calcium carbonate daily for 7 days.

the impaired dextrose tolerance of patients with diabetes or prediabetes is modified to a greater extent by the ingestion of phenobarbital than it is by placebos. Although the dextrose tolerance is increased in both groups, the increase in tolerance is definitely greater in those patients receiving phenobarbital.

Discussion. One obvious reason to explain the increased tolerance for carbohydrate manifested by most persons reappearing for a repeat dextrose tolerance test may be ascribed to the fact that most of the anxiety and nervousness exhibited by the subject during

the initial study is subsequently distinctly lessened. This is probably due to the fact that on reëxamination the individual is now acquainted with the routine and environment. Recently, Robinson

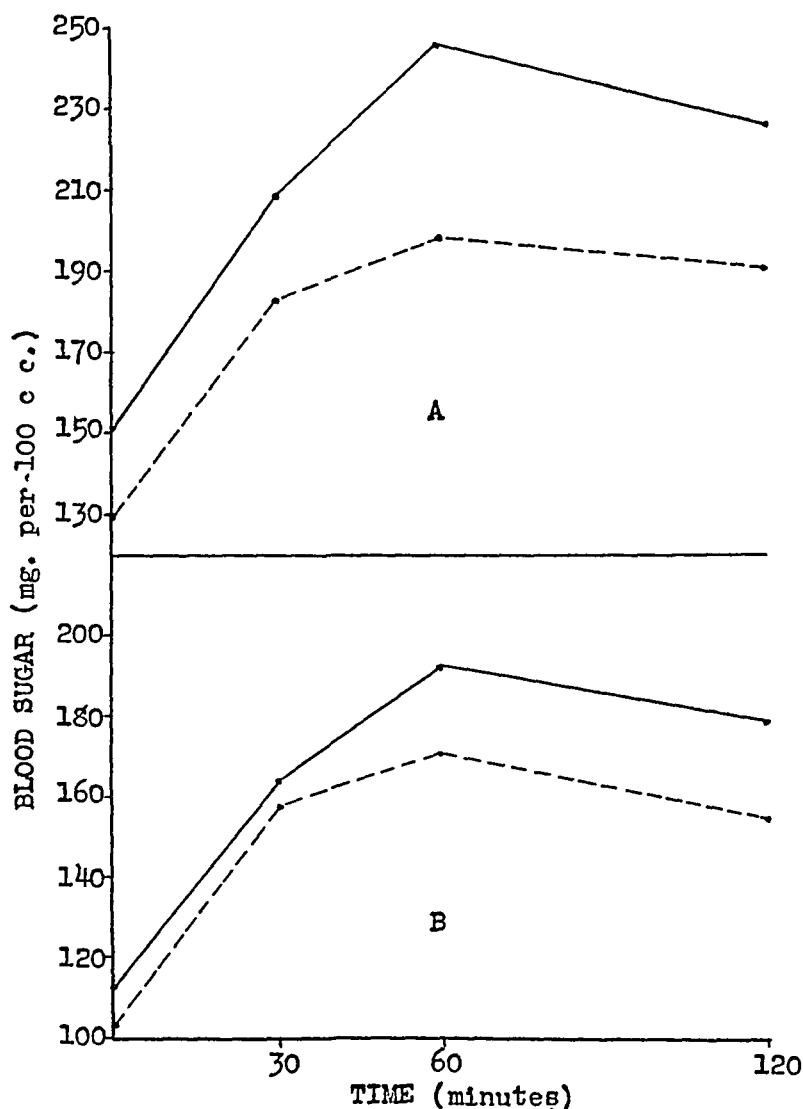


CHART 2.—A, The solid line indicates the mean dextrose tolerance curve in 11 subjects with impaired sugar tolerance prior to the ingestion of phenobarbital, and the broken line the mean dextrose tolerance curve after the ingestion of 0.2 gm. of phenobarbital daily for 7 days. B, The solid line indicates the mean dextrose tolerance curve in 8 subjects with impaired sugar tolerance prior to the ingestion of placebos, and the broken line the mean dextrose tolerance curve after the ingestion of 1 gm. of calcium carbonate daily for 7 days.

and Shelton¹⁷ have shown that overanxious types of individuals may show sufficient disturbance in the utilization of carbohydrate to impair definitely the dextrose tolerance curve.

Phenobarbital, however, appears to exert a specific effect on the impaired dextrose tolerance of diabetics and prediabetics. One can only speculate on the actual mechanism involved. Hrubetz and Blackberg^{12b} have shown that although phenobarbital is not excreted by the liver, it nevertheless depresses the glycogenolytic power of that organ as indicated by the response of the blood sugar to epinephrine. It is conceivable that this inhibition of liver glycogenolysis may account for the increased tolerance observed in patients with diabetes and prediabetes after the ingestion of phenobarbital.

Conclusions. 1. All factors which tend to modify the dextrose tolerance curve being kept as constant as possible, normal subjects or patients with diabetes or prediabetes frequently show an increased tolerance for dextrose on reëxamination 1 week after an initial study. This increase in tolerance for sugar may be ascribed to the fact that most persons reappearing for the subsequent study show a diminution in anxiety and nervousness.

2. The increase in dextrose tolerance in subjects with normal sugar tolerance receiving phenobarbital is apparent and not real; normal subjects receiving placebos show approximately the same increase in dextrose tolerance. Phenobarbital is shown, therefore, to exert no specific effect on normal dextrose tolerance.

3. The increase in dextrose tolerance in patients with impaired sugar tolerance receiving phenobarbital is greater than in those receiving placebos. Phenobarbital, therefore, affects specifically the impaired dextrose tolerance curve probably by virtue of its ability to inhibit glycogenolysis in the liver.

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DIETARY HYPERCHOLESTEROLEMIA.*

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THERE has been much controversy as to whether or not an alteration of the serum cholesterol level can be effected by dietary means. Former studies^{1,2,6-8} are at variance as to whether or not alimentary hypercholesterolemia results from the ingestion of a single fatty meal. Gardner and Gainsborough⁵ reported that no elevation of the cholesterol level could be obtained by one feeding, but that moderate changes could be produced by the prolonged feeding of diets rich or poor in fats. In a previous communication¹¹ it was reported that the serum cholesterol was not significantly altered by diets, rich or poor in fat and cholesterol in 5 of 9 patients during two 6-week periods. The fat content of the diet during the first period was 300 gm. daily and during the second less than 50 gm. daily. In 4 of the individuals a slight rise of serum cholesterol occurred during the high fat régime.

A recent article by Corwin,⁴ however, in which a marked alimentary hypercholesterolemia was produced in dogs by the feeding for 6 weeks of lecithin obtained from the adrenal gland, clearly demonstrated for the first time that the serum cholesterol could be elevated by dietary means. It was therefore considered of interest to determine: 1, if a similar alimentary hypercholesterolemia could be produced in humans; and, 2, if a prolonged alimentary hypercholesterolemia in dogs would result in arterial lesions.

1. **The Effect on the Serum Cholesterol Level of Egg Yolk Powder Feeding in Humans.** A group of 10 patients was studied. Eight had been hospitalized for rheumatoid arthritis and 2 for chronic nephritis without edema. Because pure lecithin was not available, egg yolk powder† was used as a crude source of this substance. An analysis† of the egg yolk powder showed it to contain lecithin, 14.4%; vitellin, 31.6%; nuclein, 3%; cerebrin, 0.6%; glycerophosphoric acid, 2.4%; cholesterol, 8%; fats, 40.6%; coloring matter, 1%; salts, 2%; and water, 3.6%. One hundred grams of egg

* This investigation was aided in part by a grant from the Josiah Macy, Jr., Foundation.

† R. C. Williams & Co., New York City.

yolk powder, equivalent to 31 gm. of protein and 67 gm. of fat (720 calories), in addition to the regular high caloric diet (2500 calories), was fed to the 10 patients for from 6 to 10 weeks after an initial control period of 3 to 4 weeks. A second period of egg yolk powder feeding was studied in 2 of the individuals. The egg yolk powder was fed in 50-gm. portions twice daily after being suspended in about 3 oz. of milk with sugar and vanilla added for flavoring.

Total serum cholesterol was determined weekly by the method of Bloor, Pelkan and Allen.³

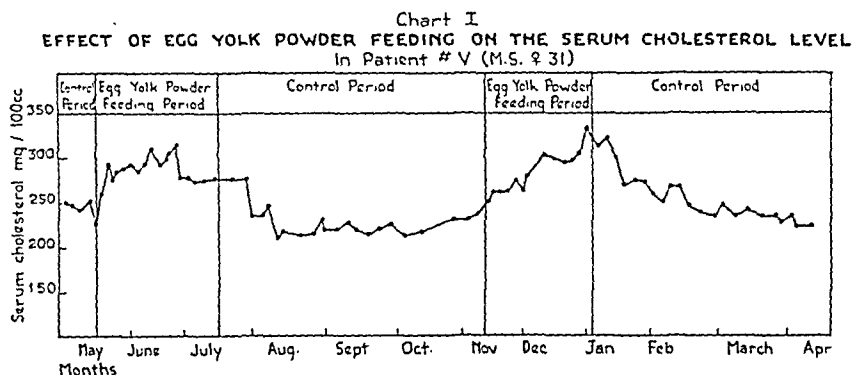
TABLE 1.—EFFECT OF EGG YOLK POWDER FEEDING ON THE SERUM CHOLESTEROL IN 10 PATIENTS.

No.	Patient.	Age.	Sex.	Diagnosis.	Control period, average.	Egg yolk powder feeding period.							Control period.	
						Weeks.					Maxi- mum increase.		Subse- quent base line.	Weeks before return- ing to base line.
						2.	4.	6.	8.	10.	Mg.	%.		
1	H.T.	31	M	Rheumatoid	195±13	245	225	235	50	25	195	2
2	E.C.	38	F	“	284± 7	360	454	330	170	58	290	2
3	A.G.	37	F	“	208± 2	243	260	260	245	...	52	25	220	3
4	J.G.	29	M	“	230± 5	280	270	315	298	278	95	41	220	1
5	M.S. (a)	31	F	“	245± 5	284	315	280	284	...	70	29	225	2
	(b)				230± 5	275	315	333	103	44	230	3
6	R.B.	34	F	“	219± 7	249	276	300	333	280	114	47	225	3
7	J.L. (a)	27	F	“	185± 5	208	220	263	281	279	96	51	200	5
	(b)				235± 5	279	290	314	276	...	80	37	225	3
8	M.S.	23	F	“	202± 6	208	215	230	240	264	62	30	206	2
				Chronic										
9	M.M.	28	F	nephritis	281±31	333	350	385	325	...	104	35	275	5
10	M.P.	18	F	“	325±44	417	417	543	218	67		

Cholesterol values expressed in mg. per 100 cc.

Table 1 contains the average serum cholesterol during the initial control period in the 10 patients studied. It also shows the serum cholesterol determinations after 2, 4, 6, 8, or 10 weeks of egg yolk powder feeding with the maximum increase and the maximum per cent increase. The subsequent base line attained by serum cholesterol and the number of weeks required to reach this level are also recorded. From this table it can be seen that during the initial control period, the serum cholesterol remained relatively constant in 8 of the 10 patients. The deviation from the average varied from 2 to 13 mg. This finding has been commented upon previously.^{10,11} The 2 patients in whom the serum cholesterol level fluctuated widely were cases of chronic nephritis. Edema was not present in these individuals. It can also be seen from Table 1 that following the ingestion of egg yolk powder the serum cholesterol level in each patient increased, reaching a maximum in 2 to 8 weeks. The increase in serum cholesterol varied from 50 to 218 mg., the average

increase being 101 mg. The percentage increase in serum cholesterol varied from 25% to 67%, the average being 41%. After discontinuance of egg yolk powder feeding, the serum cholesterol level gradually diminished, returning to a relatively constant base line in from 1 to 5 weeks. Chart 1 illustrates the variation in the serum cholesterol level during and subsequent to 2 periods of egg yolk powder feeding in Patient 5.



2. Effect of Prolonged Egg Yolk Powder Feeding in Dogs. In the second phase of this study 100 gm. of egg yolk powder were fed daily to 4 mongrel dogs, 3 male and 1 female. This was added to 200 gm. of regular dog food which contained 20% protein, 60% carbohydrate, and 2% fat. There were four periods of egg yolk powder feeding for each animal totalling from 44 to 56 weeks. Four control periods were interspersed between the egg yolk powder feeding periods and varied from 4 to 6 weeks each.

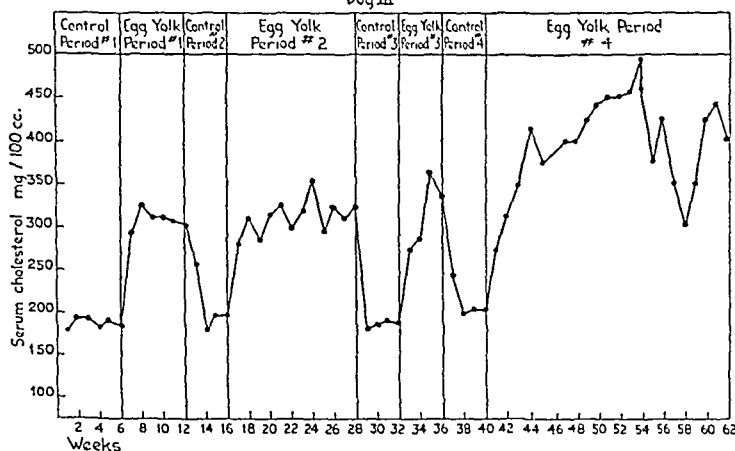
Serum cholesterol determinations were done weekly by the method of Bloor, Pelkan and Allen.³ At the end of the experiment the animals were sacrificed and autopsied.

Table 2 records the serum cholesterol determinations obtained during the control and egg yolk powder feeding periods, 4 of each, in the animal experiment. From the data presented it is seen that in each of the 4 dogs the serum cholesterol increased following the ingestion of egg yolk powder. The maximum increase varied from 155 to 251 mg., with an average of 203 mg. Chart 2 illustrates the fluctuation of serum cholesterol level in Dog 3 during the control and egg yolk powder feeding periods.

The animals were sacrificed at the end of the experiment by air embolus. Gross examination of the organs revealed no structural changes beyond wrinkling of the intima of the aorta in 2 of the 4 instances. This was confined to the arch and ascending portion of the aorta. Microscopic sections showed only one area of intimal fibrous thickening in one aorta. Anisotropic fat and cholesterol clefts were not present in this lesion. Lipoid infiltration was not present in the liver, lung, kidney or spleen.

TABLE 2.—EFFECT OF EGG YOLK POWDER FEEDING ON THE SERUM CHOLESTEROL LEVEL IN DOGS.

	Dog 1.	Dog 2.	Dog 3.	Dog 4.
Control period No. 1:				
No. of weeks	6	6	6	6
Average serum cholesterol .	200±7	168±10	190±5	333±6
Egg yolk feeding period No. 1:				
No. of weeks	6	6	6	6
Highest serum cholesterol .	333	278	324	417
Control period No. 2:				
No. of weeks	4	4	4	4
Base line serum cholesterol .	188	151	184	312
Egg yolk feeding period No. 2:				
No. of weeks	12	12	12	12
Highest serum cholesterol .	312	245	355	500
Control period No. 3:				
No. of weeks	4	4	4	4
Base line serum cholesterol .	196	175	185	334
Egg yolk feeding period No. 3:				
No. of weeks	4	4	4	4
Highest serum cholesterol .	282	246	384	500
Control period No. 4:				
No. of weeks
Base line serum cholesterol .	211	158	200	368
Egg yolk feeding period No. 4:				
No. of weeks	34	34	22	34
Highest serum cholesterol .	400	323	497	584
Total no. of weeks of egg yolk feeding	56	56	44	56
Maximum increase in serum cholesterol, all periods . .	200	155	207	251

Chart II
EFFECT OF EGG YOLK POWDER FEEDING ON THE SERUM CHOLESTEROL LEVEL
Dog III

Comment. An alimentary hypercholesterolemia has been produced in humans and in dogs by feeding egg yolk powder for periods varying from a month to a year. The lecithin content of the egg yolk powder appears to be the important factor in the elevation of the serum cholesterol because comparable effects were not obtained by diets rich in fat and cholesterol even with the addition of 10 gm. of crystalline cholesterol daily.¹¹ All except 1 of the patients gained

body weight during the egg yolk powder feeding period. This finding will be described elsewhere.*

The elevations in serum cholesterol occurring in dogs as a result of egg yolk powder feeding were not as great as those obtained by Corwin⁴ when feeding 50 gm. of pure lecithin daily. However, the 100 gm. of egg yolk powder contained only 14 gm. of lecithin. At postmortem examination no atheromatous lesions of the aorta or coronary arteries were found. Indeed, experimental lesions of this nature have never been produced in the dog. However, the elevations of the serum cholesterol in these animals did not compare with those high levels obtained in rabbits by cholesterol feeding,⁹ and, therefore, the possibility that experimental atherosclerosis in dogs would occur in the presence of more marked hypercholesterolemia is not excluded.

Conclusions. 1. Ten patients, 8 with rheumatoid arthritis and 2 with chronic nephritis, were fed egg yolk powder containing 14% lecithin for 6 to 10 weeks. The serum cholesterol in each increased from 50 to 218 mg. with an average rise of 101 mg.

2. A hypercholesterolemia was produced in 4 dogs by the feeding of egg yolk powder for from 44 to 56 weeks. The elevation in serum cholesterol ranged from 155 to 251 mg.

3. The moderate hypercholesterolemia in 4 dogs did not result in significant arterial lesions.

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THE INCIDENCE OF CERTAIN SIGNS AND SYMPTOMS AT VARIOUS LEVELS OF BASAL AND TOTAL RESTING METABOLISM.

AN ANALYSIS OF 1000 CASES.

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ALTHOUGH it is recognized that certain signs and symptoms are generally associated with certain levels of metabolic rate, it is rather difficult to find from the literature their average incidence

* Unpublished data.

at different rate levels. Believing that a statistical analysis of this question would be of value, a study has been made of 1000 records of individuals having had carefully performed basal metabolisms.

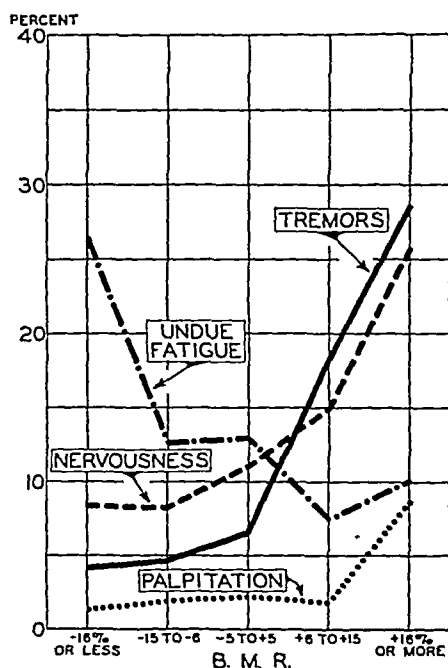
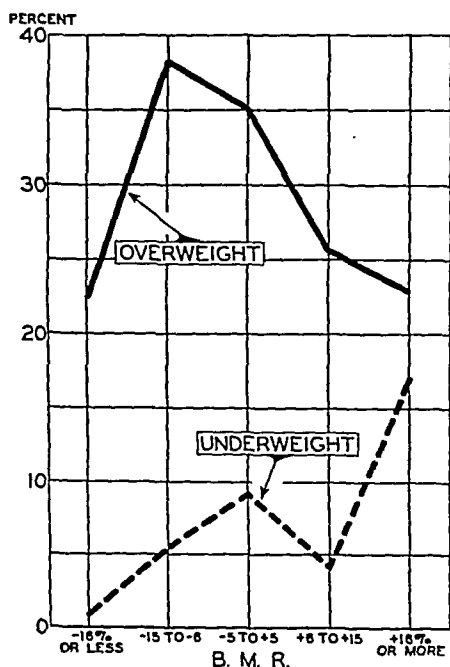
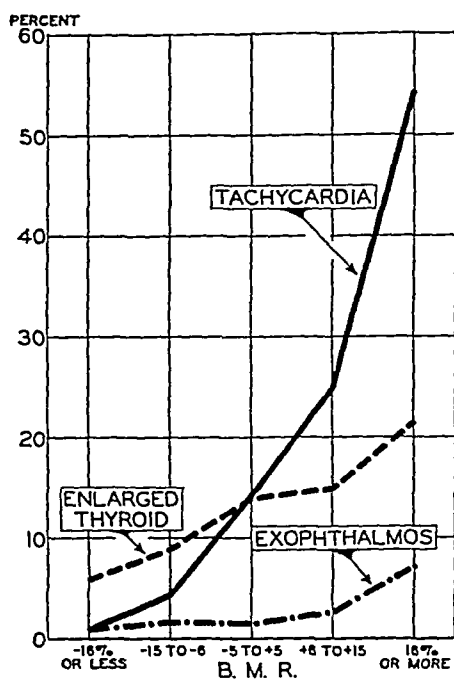
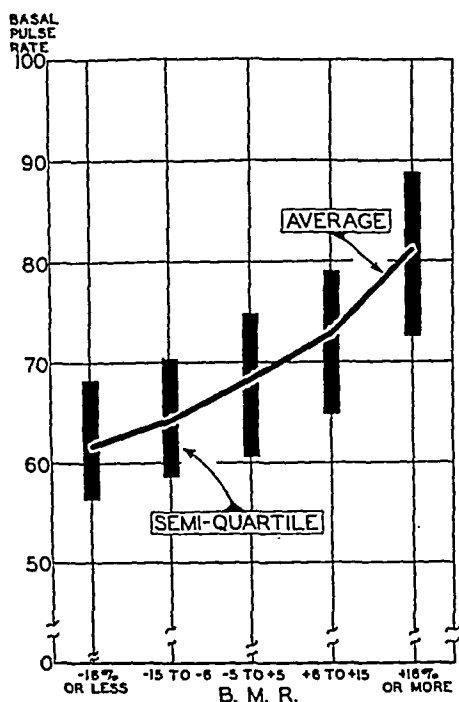


CHART 1.—Physical findings and symptoms in relation to basal metabolic rate of 1000 cases.

The metabolic rates have been given the primary consideration and such findings as pulse rate, tachycardia, enlarged thyroid, exophthalmos, overweight, underweight, tremors, undue fatigue, "nervousness" and palpitation have been correlated with the basal rate levels without regard to the diagnosis. The results are portrayed in Chart 1.

Basal metabolic rates have been grouped as follows: -16% or less, -15 to -6% , -5 to $+5\%$, $+6$ to $+15\%$, and $+16\%$ or more. The distribution of cases is shown in Table 1.

TABLE 1.—DISTRIBUTION ACCORDING TO BASAL METABOLIC RATES OF 1000 CASES.

Groups.	Males.	Females.	Total.	Average B.M.R., %.
-16% or less	54	67	121	-19.2
-15 to -6%	142	187	329	-10.0
-5 to $+5\%$	140	219	359	-0.9
$+6$ to $+15\%$	46	75	121	$+9.5$
$+16\%$ or more	30	40	70	$+27.9$

Although only the semi-quartile range of basal pulse rates has been listed, one is impressed immediately with the wide variation which exists at each level of basal metabolism. Even though the average trend is regularly upward, this chart represents the futility of any attempt to estimate basal metabolism from the pulse rate alone.

For the purposes of this study tachycardia was defined as a pulse rate of 80 or above under basal conditions. It will be noted that the incidence of tachycardia increased sharply with each increased level of basal metabolic rate.

Enlargement of the thyroid gland also increased steadily but even in the highest level of $+16\%$ or more (the average was $+27.9\%$), where thyrotoxicosis was probably the main cause of the elevated metabolism, the thyroid enlargement was present only to the extent of 21.4% of the group. Exophthalmos was likewise of low incidence, and reached 7.1% of the group. Exophthalmos was likewise of low incidence, and reached 7.1% at the highest average metabolic level.

The incidence of overweight was greatest in the basal metabolic level of -15 to -6% , where it reached a level of 38.3% . Oddly enough, at a lower level of metabolism, the incidence was only 22.3% . Above the metabolic level of -15 to -6% there was a steady decline in the incidence of overweight. The fact is often overlooked that in individual cases, high levels of basal metabolism may be and frequently are associated with gross overweight. In this series the group having the highest level still showed an overweight incidence of 22.9% . The highest incidence of *normal* weight (not depicted in the chart) was 80% , and was found at the lowest metabolic level. Thereafter the percentages were between 53 and 70

and showed no definite trend. The underweight group increased irregularly from the lowest to the highest level of basal metabolism.

Among the subjective symptoms, palpitation did not become unduly evident until the highest level of basal metabolism was reached, where 8.6% of the series complained of this symptom. Tremors became a pronounced symptom only at the abnormally high levels, where the maximum was 28.6%. "Nervousness" followed the same trend as did the tremors. Undue fatigue was most noticeable at the lowest level of basal metabolism where it was present in 26.4% of the series. It showed a marked decline to a minimum of 7.4% in the +6 to +15% level, from which point it began to show an upward trend. It is probable that a series with larger numbers of abnormally high metabolic rates would show a still further elevation in this symptom.

In addition to the basal rates (which represent heat production *per unit of body surface* in percentage of normal), a study has been made of the same list of symptoms and findings with reference to the total resting metabolism (total heat production) in that portion of the thousand whose basal rates were between -10 and +10% of normal. It is perhaps not sufficiently well recognized that there is a difference between basal metabolism as reported by the laboratory and the total resting metabolism. This distinction has been emphasized previously.² It should be borne in mind that whereas "basal" metabolism represents only the unit heat production, the total metabolism represents the heat production of the body as a whole, both expressed in percentage of normal. These percentages will be identical when the weight is normal. In case of overweight the total resting metabolism will exceed the basal metabolism directly as the degree of overweight. An increased surface area means a greater total heat production even though the unit heat production is within normal limits. The distribution of the 630 cases with basal rates of -10 to +10% is shown in Table 2.

TABLE 2.—DISTRIBUTION ACCORDING TO TOTAL RESTING METABOLISM OF 630 CASES WITH BASAL RATES OF -10 TO +10% OF NORMAL.

Group.	Males.	Females.	Total.	Average T.H.P., %.
-6% or less	53	73	126	- 9.1
-5 to +5%	119	170	289	- 1.0
+6 to +15%	58	96	154	+ 9.6
+16% or more	16	45	61	+21.3

It has been stated by Evans and Strang^{1,3,4} that there are frequently found in the obese many of the signs which are associated with the high basal metabolic levels of hyperthyroidism, since the rate of total heat production is elevated. However, the frequency with which various signs and symptoms make their appearance was not stated. Our study includes only those individuals whose basal metabolisms were within normal limits, but many of whose

total heat productions were distinctly increased. The results of this study are set forth in Chart 2.

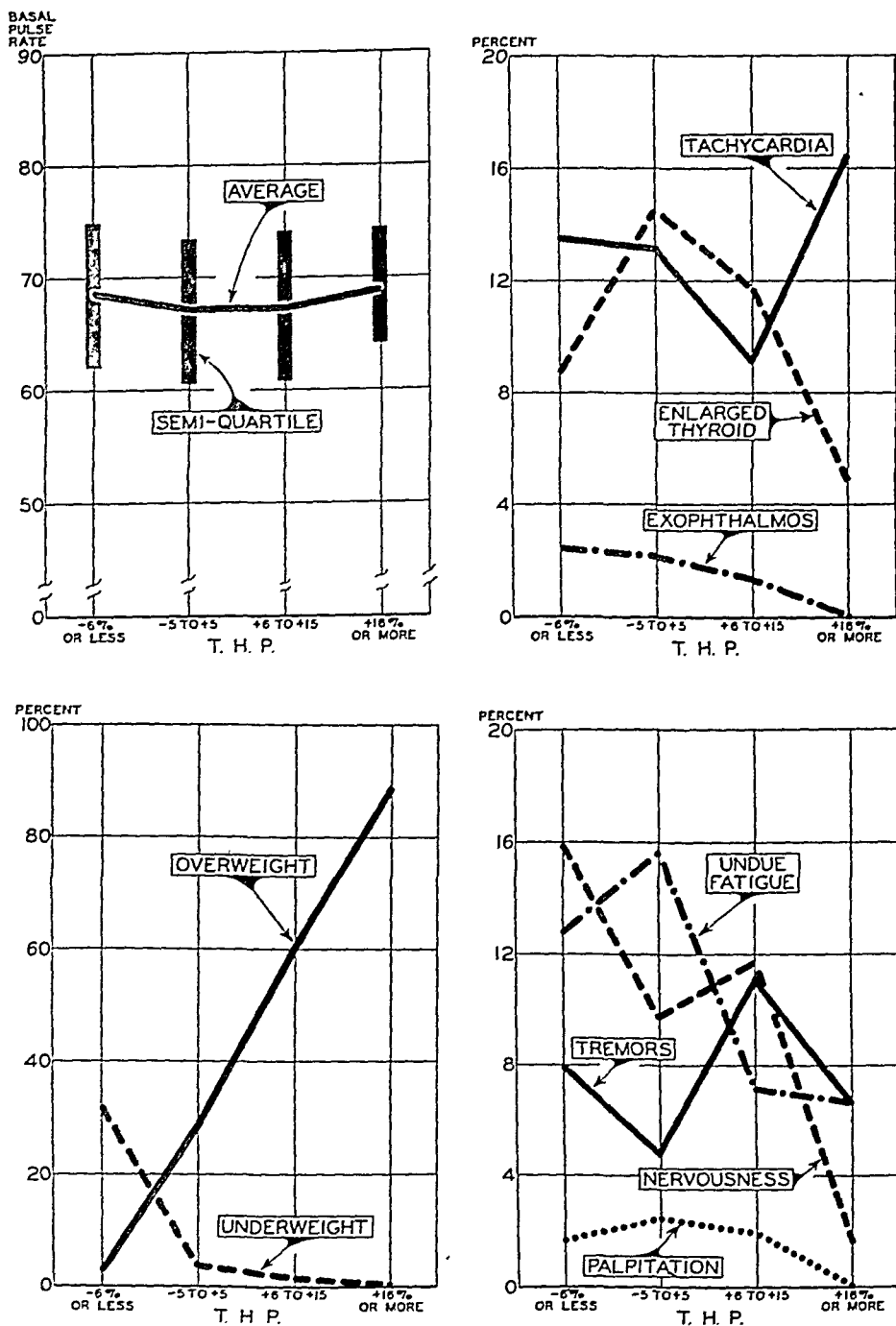


CHART 2.—Physical findings and symptoms in relation to total resting metabolism of 630 cases with basal rates of -10 to $+10\%$ of normal,

In view of the statements by Evans and Strang^{1,3,4} and the experience of the writer, it was expected that there would be found in the study of the total resting metabolic rates a picture somewhat similar to that presented by the basal metabolic rates. Definitely abnormal basal metabolic rates were excluded in order to eliminate their influence upon the total heat production.

As we study the incidence of signs and symptoms in Chart 2, it is evident that the same trends found in Chart 1 are not present. Average pulse rates were almost the same at the various levels of total heat production with no definite trend manifest. The incidence of tachycardia which first showed a decline in the three lower levels increased sharply at the highest level which represented the greatest degree of overweight. The incidence of enlarged thyroid was the reverse of that seen in Chart 1, as was also the incidence of exophthalmos.

There was of course a very definite, sharp upward trend in the incidence of overweight, simply because the increase in total heat production, where the basal metabolic rate is normal, depends upon the presence of overweight.

Undue fatigue declined sharply from the lowest level to the highest as did also the incidence of "nervousness." Tremors were irregular and showed no definite trend. Palpitation was less evident at the highest level.

It is evident that relevant signs and symptoms in this series did not follow the trends at different rates of *total resting* metabolism that were seen at the same levels of *basal* metabolism when the cases with abnormal basal rates were excluded. It is possible in a series having more pronounced degrees of overweight which would of course show still larger increases in the total heat production, that a greater trend toward abnormal signs and symptoms would be manifested. In this study, however, there were no similar trends in physical signs and subjective symptoms in association with increasing degrees of total resting metabolic rate levels.

Summary and Conclusions. 1. Pulse rates together with the incidence of tachycardia, enlarged thyroid, exophthalmos, overweight, underweight, tremors, undue fatigue, "nervousness" and palpitation have been studied in association with different levels of basal metabolic rate in a series of 1000 cases.

2. Pulse rates, tachycardia, thyroid enlargement, exophthalmos, "nervousness," tremors, palpitation and underweight increased in varying degrees with increasingly higher levels of basal metabolic rate, while fatigue and overweight showed predominantly an opposite trend.

3. Contrary to expectations the same trends were not found in association with increasingly higher levels of total resting metabolism. Although such pertinent findings and symptoms may be

prevalent in individual cases, particularly of the more obese type, they were not found to be generally characteristic.

Acknowledgment is made to Dr. H. J. Johnson who first suggested the value of this study, and to Miss M. F. Kelley and Mr. H. A. Ley, Jr., who did much of the statistical work.

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PROTHROMBIN STUDIES IN PULMONARY TUBERCULOSIS.*

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IN the study of tuberculous patients, various laboratory tests for determining the degree of resistance and toxemia and of estimating the response to treatment have been employed. As yet no single laboratory method has proven satisfactory for this purpose. Of the procedures used, the erythrocyte sedimentation rate, the leukocyte index (Schilling) and the leukocyte-monocyte ratio (Medlar) have been the most widely used. At times certain conclusions can be drawn from a combination of such tests, particularly in objectively confirming clinical impressions regarding toxicity and reaction to treatment. In the present study an attempt is made to evaluate a comparatively new method which may be of aid in this connection.

The prothrombin coagulation time of the blood plasma has been extensively applied in the study of blood dyscrasias and hemorrhagic disorders in which prothrombin deficiency might be a factor. It has been fairly well established that the liver is essential for the maintenance of normal prothrombin values^{2,3} and probably is the chief site of formation of prothrombin.⁸ Other implications have been suggested, including the possibility that prothrombin activity might serve as an index of liver function and Wilson⁹ has noted that it frequently parallels the hippuric acid excretion test for liver function. However, it is hardly conceivable that prothrombin determination would be a satisfactory method of evaluation of all the functions of the liver even though it is a sensitive reflector of liver damage in diseases directly involving the liver.⁹ At the same time it is possible that changes may occur in the blood stream itself which might affect the circulating prothrombin without directly

* A part of the expense of this study was defrayed by a grant from the Joseph V. Horn Fund.

influencing its production in the liver. The present study suggests this possibility.

Material and Method. With the above consideration in mind the present study was undertaken for the purpose of determining what changes, if any, occur in the prothrombin of the plasma in pulmonary tuberculosis in various stages of the disease. Seventy tuberculous patients have been studied. There are included a number of patients who have undergone collapse therapy, either artificial pneumothorax or thoracoplasty, some early cases prior to active treatment and some far advanced cases with either progressive caseating lesions or chronic fibro-ulcerative lesions. Several patients with such complications of artificial pneumothorax as tuberculous and mixed infection empyema are included.

The procedure for determining the prothrombin of the blood plasma consists of the quantitative method of Quick,⁶ in which oxalated plasma is recalcified in the presence of tissue thromboplastin obtained from rabbit brain. The thromboplastin solution is prepared by centrifugation from a thymolized normal saline suspension and standardized each time it is used by means of three normal control subjects. The results are reported in percentage of average normal. In many instances several determinations were made in the same patient, particularly when a change in the treatment was undertaken or when some alteration in the clinical course occurred. The erythrocyte sedimentation rate and vital capacity were determined for each patient. Complete clinical studies including routine chest Roentgenograms and leukocyte counts were carried out in all patients.

Findings. For statistical analysis, the patients are divided according to the prothrombin values into 4 arbitrary groups (Table 1), the first composed of those having a prothrombin value of over 100%, the second from 80% to 99%, the third from 60% to 79% and the fourth less than 60%. Group 1 includes 16 patients. Of these, 12 were patients who had had a satisfactory pneumothorax or thoracoplasty and the disease was almost or completely under control. Two patients had old inactive, fibrotic lesions with negative sputum who could not be considered as definitely arrested but who were quiescent. The other 2 had partly effective pneumothorax with symptomatic and clinical improvement but without completely controlling the disease. One (R.P.) subsequently developed a spontaneous pneumothorax followed by a tuberculous effusion and when this occurred there was a sharp drop in the prothrombin level from 150% to 49%.

In Group 2, there were 22 patients. Of these, 11 had pneumothorax but only 2 of these had completely controlled tuberculosis, the others having been early cases of pneumothorax or patients with active disease in the opposite lung. Seven had some form of surgical collapse but 6 were considered as still having active disease. Two had low-grade activity with partial collapse by pleural effusion and 2 had long-standing chronic fibrotic tuberculosis with an essentially benign clinical course. One patient included in this group (E.L.) developed tracheal lesions and reactivation of an apparently quiescent focus in the left lung with a drop in the prothrombin value from 85% to 70%. Another (F.K.) had an unsatisfactory

pneumothorax, the abandonment of which resulted in a decrease of the prothrombin activity from 85% to 64%.

TABLE 1.—COMPOSITE RECORD OF RESULTS INCLUDING SEDIMENTATION TIME AND VITAL CAPACITY.

Group 1.						
Case.	Date,*	Quantitative prothrombin.			Sed.† rate.	Clinical condition.
		Control time.	Patient's time.	%.		
W.K.	9/21	15.5	14.1	180	2800	7 Thoracoplasty with arrest; working.
M.H.	7/19	20.5	19.3	165	1500	30 Old fibrotic type; negative sputum.
G.T.	3/26	14.5	13.4	160	3100	4 Good pneumothorax; cavity closed.
R.P.	4/12	16.5	15.6	150	3000	20 Early pneumothorax; cavity open.
	9/18	16.0	19.7	49	1500	30 Following spontaneous pneumothorax with tuberculous effusion.
M.G.	9/21	15.5	14.6	150	900	12 Old fibrotic type; negative sputum.
C.L.	4/12	16.5	15.7	145	900	9 Thoracoplasty and apparent arrest.
E.T.	9/9	19.0	18.4	135	1400	7 Thoracoplasty; low-grade activity.
J.S.	9/13	20.5	19.9	135	3500	6 Good pneumothorax; working.
K.S.	4/12	16.5	15.9	132	1000	22 Extrapleural pneumothorax; sputum neg.
M.T.	4/12	16.5	16.1	120	800	10 Bilateral pneumothorax; sputum neg.
M.W.	4/5	16.5	16.3	110	1000	28 Early pneumothorax.
M.H.	9/27	16.5	16.3	110	1000	9 Thoracoplasty, almost quiescent.
A.F.	4/2	14.0	13.7	105	1300	8 Good pneumothorax; sputum neg.
J.K.	3/26	14.5	14.4	105	2700	6 Good pneumothorax; working.
M.O.	3/29	14.0	14.1	100	1200	21 Thoracoplasty for tuberculous empyema.
W.S.	4/19	16.0	16.0	100	2400	9 Pneumothorax, partial control, sputum.
Group 2.						
A.C.	3/23	14.5	14.7	98	1700	8 Good pneumothorax; working.
F.A.	9/18	16.0	16.4	96	3000	12 Early pneumothorax; disease controlled.
M.H.	4/9	15.5	15.8	95	1400	5 Good pneumothorax; sputum negative.
M.K.	4/5	16.5	16.8	95	800	18 Fibrotic type, low grade; phrenic.
M.K.	9/19	19.0	19.5	93	1500	25 Early pneumothorax; cavity open.
K.M.	4/9	15.5	16.0	93	600	29 Extrapleural pneumothorax; active.
F.W.	3/26	14.5	15.2	90	1900	6 Good pneumothorax; working.
L.S.	10/21	17.0	17.5	92	2400	22 Chronic fibroid type; sputum positive.
M.P.	4/9	15.5	16.1	91	2100	30 Chronic fibroid type; sputum positive.
F.W.	4/5	16.5	17.1	91	1600	30 Pneumothorax; opposite side active.
D.I.	4/11	16.5	17.2	90	1500	23 Pneumothorax and thoracoplasty.
E.H.	9/9	19.0	19.7	90	1670	25 Early pneumothorax.
P.C.	3/26	14.5	15.2	90	1700	27 "Late pneumothorax" type; sputum negative.
L.W.	4/2	14.0	14.7	89	1300	25 "Late pneumothorax" type; sputum negative.
B.C.	3/26	14.5	15.3	89	1800	21 "Late pneumothorax" type; sputum negative.
M.O.	4/2	14.0	14.9	87	1000	25 Pneumothorax; opposite side active.
H.L.	4/2	14.0	14.9	87	950	15 Pneumothorax and thoracoplasty.
E.M.	4/5	16.5	17.5	85	2100	30 Low-grade activity, mod. advanced.
E.L.	4/9	15.5	16.5	85	1700	15 Right pneumothorax; left fibrosis.
	10/18	19.0	21.1	70	1200	23 Tuberculous tracheitis developed.
F.K.	4/9	15.5	16.5	85	800	32 Rt. thoracoplasty; left pneumothorax.
	10/11	19.0	21.5	64	1300	30 Left lung reexpanded; open cavities.
M.A.	3/23	14.5	15.5	85	1500	3 Thoracoplasty; low-grade activity.
T.C.	3/26	14.5	15.8	81	1700	15 Thoracoplasty for tuberc. empyema.
Group 3.						
I.L.	10/2	17.0	18.5	79	2000	8 Early pneumothorax; incomplete collapse.
L.M.	4/4	14.0	15.6	79	800	21 Right pneumothorax; left open cavity.
L.W.	9/18	16.0	17.5	78	2800	18 Spontaneous pneumothorax; pleurisy.
A.D.	4/19	16.0	17.6	77	1200	25 Far advanced active tuberculosis.
H.H.	4/18	16.0	17.6	77	1700	29 Tbc. empyema; bronchopleural fistula.
F.H.	3/26	14.5	16.1	76	1800	21 Far advanced active tuberculosis.
L.F.	3/26	14.5	16.2	75	1500	28 Tbc. empyema; pleurocutaneous fistula.
C.M.	7/19	20.5	22.3	74	1300	7 Postoperative thoracoplasty.
F.G.	10/8	16.5	18.6	70	3700	13 Early tuberculosis with hemoptysis.
	10/25	18.0	16.1	225	3700	13 Hemoptysis stopped; cavity previously seen no longer apparent.
M.A.	9/27	16.5	18.6	70	850	30 Far advanced active tuberculosis.
J.M.	3/23	14.5	16.7	69	1000	12 Tbc. empyema; thoracoplasty.
E.T.	9/9	19.0	21.2	68	2300	26 Active fibroid tuberculosis; cavity.
R.A.	4/9	15.5	17.8	67	1500	26 Pneumothorax; opposite side active.
A.T.	9/21	15.5	17.7	66	2600	32 Early chronic exudative tuberculosis.
M.B.	3/29	14.0	16.6	63	2300	27 Early chronic exudative tuberculosis.
A.H.	7/12	18.0	20.7	61	2100	25 Far advanced fibroid tuberculosis.
J.S.	7/12	18.0	20.7	61	1900	25 Far advanced ulcerative tuberculosis.

Case.	Date,* 1940.	Quantitative prothrombin.			V.C.	Sed.† rate.	Clinical condition.
		Control time.	Patient's time.	%.			
Group 4.							
G.O.	3/23	14.5	17.4	59	1800	24	Tbc. empyema; opposite side active.
H.W.	3/23	14.5	17.4	59	1900	11	Exudative tuberculosis; hemoptysis.
I.L.	10/8	16.5	19.8	53	1600	29	Far advanced tuberculosis; effusion.
H.H.	3/23	14.5	17.7	53	2000	17	Right thoracoplasty; left pneumothorax.
C.M.	9/13	20.5	23.9	51	2100	30	Right pneumothorax; activity on left.
C.M.	3/29	14.0	17.4	51	1600	30	Mixed infection empyema.
P.B.	7/12	18.0	21.5	50	3100	30	Pulmonary and urogenital tuberculosis, far advanced.
S.E.	10/2	17.0	20.8	49	1600	18	Chronic fibroid tuberculosis, atelectasis.
C.S.	10/11	19.0	23.0	48	700	30	Chronic fibroid tuberc. and atelectasis.
A.C.	9/13	20.5	24.9	47	1800	25	Acute pleurisy with hemorrhagic effusion.
M.V.	7/12	18.0	22.5	47	1600	15	Pneumothorax; hemoptysis.
J.T.	10/18	19.0	23.5	46	2800	24	Exudative tuberculosis with hemoptysis.
M.G.	10/8	16.5	21.3	45	1100	22	Exudative tuberculosis on left side.
	10/18	19.0	21.2	68	700	22	Pneumothorax started on left.
W.P.	10/2	17.0	23.4	40	2500	28	Bilateral chronic active tuberculosis.
M.R.	4/5	16.5	24.1	36	800	26	Far advanced bilateral tuberculosis with atelectasis.

* Dates given are for prothrombin determinations.

† In some instances, dates of sedimentation and vital capacity determinations do not exactly coincide with those of prothrombin determinations. Sedimentation recorded in millimeters in 1 hour.

There were 17 patients in Group 3. Seven of these had thoracoplasty with the activity not yet controlled and of these, 3 had tuberculous empyema. Four had pneumothorax with persistent pleurisy or activity in the opposite lung. Five had far advanced disease without collapse therapy. One was an early case with hemoptysis (F.G.). Following complete rest in bed during which time the hemoptysis was controlled and the lesion showed signs of clearing, there was a marked increase in the prothrombin from 70% to 225%.

Group 4 was made up of 15 patients. There were 8 with far advanced active disease with unsatisfactory or no collapse or with activity in the opposite lung. Most of the patients with acute caseous tuberculosis were found in this group. Three patients had hemoptysis and 2 of them had active disease with positive sputum. One had severe pleurisy with a bloody effusion and one had thoracoplasty on the right with artificial pneumothorax on the left. Two had empyema, 1 tuberculous and 1 mixed infection. One patient (M.G.) who, 6 years previously, had a right thoracoplasty, developed a widespread and fairly acute type of disease in the left lung. The prothrombin was 45% and 1 week after initial pneumothorax on the left side the value was 68%.

The sputum studies in the 4 groups (see Table 1) are indicated in Table 2, showing the relationship between the patients with positive sputum and the prothrombin values. In Group 1, with normal or increased prothrombin values, only 31% had positive sputum and in Group 4, with markedly decreased prothrombin values, 87% were positive. In Groups 2 and 3, 78% and 83% respectively had positive sputum, showing the tendency toward progressively lowered prothrombin values in the groups with more active disease.

The sedimentation rate and vital capacity determinations have been included in Table 1, in order to point out the relationship

between those values and the prothrombin levels. It is found that in Group 1 the sedimentation is normal in all patients who are considered arrested and who are employed. A few in whom the prothrombin was above normal showed sedimentation rates slightly more rapid than normal. This was particularly true of the patients with early pneumothorax or thoracoplasty in whom the disease was not under control. One patient (W.S.) had a normal sedimentation rate and 100% prothrombin but still had active tuberculosis with unsatisfactory collapse. In Group 2, the sedimentation rates of all the patients were rapid with the exception of the 3 with good pneumothorax (M.H., A.C., F.W.) who were in this group and the 1 patient (T.C.) who had just recently had a three-stage thoracoplasty for tuberculous empyema. In Group 3, most of those with active tuberculosis had rapid sedimentation rates but 2 who had pneumothorax or thoracoplasty had normal values. In Group 4, the sedimentation time was rapid in all except 2 cases and both of these were patients with hemoptysis, one with active disease (H.W.) and the other with pneumothorax (M.V.) and hemoptysis with no evidence of active disease. In the latter case the hemoptysis was believed to have resulted from bronchial changes of a mechanical nature related to the pneumothorax. It appears from these findings that the sedimentation rates and the prothrombin values parallel each other but there are enough variations both ways to rule against drawing any positive conclusions from either test.

TABLE 2.—SPUTUM STUDIES OF PATIENTS IN GROUPS OF TABLE 1.

	Positive sputum.		Negative sputum.	
	No.	%.	No.	%.
Group 1	5	31	11	69
Group 2	17	78	5	22
Group 3	14	83	3	17
Group 4	13	87	2	13

The reduction of vital capacity is not alone responsible for the increased prothrombin level in the tuberculous patients in whom this condition was present. Reference to Table 1 shows that there are many patients with low vital capacities who at the same time have decreased prothrombin values. Most of these have incompletely effective collapse or persisting toxicity from other causes.

Discussion. From a study of the findings, certain trends become apparent. It is noted that the patients who have effective collapse therapy have a normal or increased prothrombin level and in those with partly successful collapse treatment the values approach normal except in the presence of such complicating factors as activity in the opposite lung, pleurisy, tuberculous empyema or hemoptysis. The patients with low-grade activity or chronic

fibrotic tuberculosis also show prothrombin values which approach normal. On the other hand, the patients with the more severe or acute forms of pulmonary tuberculosis tend to have low values, while those with chronic ulcerative lesions have moderately reduced values. In the chronic ulcerative cases with early or unsatisfactory collapse treatment, the prothrombin approaches normal even if the disease is not adequately controlled.

One of the most interesting observations is the increased rapidity of prothrombin clotting in the effective collapse therapy group. A possible explanation of this finding is suggested by the studies of Andrus *et al.*¹ who found a fall in prothrombin activity in the blood coming from the lungs of dogs as compared with that entering the lungs. No such fall was noted between the blood entering and leaving any other organ. They suggest the conclusion that prothrombin is destroyed in the lungs. If this is the case, collapse therapy might sufficiently alter the character and rate of circulation through the lungs to affect significantly the destruction of prothrombin. The reduction in circulation in a collapsed lung has been previously discussed^{4,5} and is accepted as one of the effects of collapse therapy. It is quite conceivable that this circulatory change could prevent the destruction of prothrombin which normally occurs in the lungs according to present evidence.

There is no definite parallelism between the degree of collapse and the actual prothrombin value, a small amount of collapse producing the same increase in prothrombin as a marked collapse, provided the lesions are under control. This again is probably dependent upon the circulatory physiology of collapse therapy, a rather marked reduction in circulation which is out of proportion to the reduction in vital capacity taking place soon after the lung is collapsed.

In the patients with active disease with diminished prothrombin, other factors probably play a large part. The fact that the reduction of vital capacity is not always associated with increased prothrombin values strongly supports this conclusion. Of these factors, toxemia appears to be most important and it appears from a study of the patients in Groups 3 and 4 that the decrease in prothrombin is almost directly proportional to the degree of toxemia. The decreased toxic absorption which occurs in collapse therapy has often been observed clinically and probably is associated with the decreased circulation and decreased aeration of the lung which may have a deleterious effect on the tubercle bacilli. The increase in the rapidity of prothrombin clotting in collapse therapy suggests that the toxins may have played a part in decreasing the amount of prothrombin. It may even suggest that the toxic products themselves have a destructive effect on the circulating prothrombin.

The relationship between prothrombin and activity of the tuberculous process is further suggested by the sputum examinations. Table 2 indicates the progressive increase in the number of patients with positive sputum from Group 1 to Group 4. Most of the patients with negative sputum appear in Group 1, a few in Group 2 and very few in Groups 3 and 4. The importance of this finding becomes apparent when coupled with the other observations.

To determine whether the prothrombin deficiency in the patients with far advanced disease responds to vitamin K, 3 patients (H.H., I.L., C.S.) were given oral treatment with 2-methyl-1, 4-naphthoquinone. Doses up to 6 mg. daily were used and the prothrombin checked repeatedly. In none of the cases studied was any increase in prothrombin noted as a result of the therapy.

Of special interest are the patients with hemoptysis. Several patients with this symptom had fairly low prothrombin values (59%, 47%, 46%) but none of these appeared to be ill enough to account for such a marked decrease in prothrombin as compared with other patients in the group. The sedimentation rate was not as rapid in these patients as in others with comparable prothrombin levels. It is thus possible that the hemoptysis had something to do with the low prothrombin values. On the other hand, it is unlikely that the low prothrombin values could have been responsible for the hemoptysis from a standpoint of clotting deficiency, with the possible exception of the last patient in Group 4 (M.R.) who died during a massive hemoptysis. The last determination about 2 weeks before death revealed a prothrombin level of 36%. She was extremely toxic with tuberculous tracheobronchitis, bronchial stenosis and atelectasis and this may have accounted for sufficient decrease in prothrombin to prevent formation of a clot when a small vessel was eroded. In the patient with early tuberculosis (F.G.) who showed marked increase in prothrombin following cessation of the hemoptysis, an overcompensatory mechanism is suggested.

Since this study was undertaken, there have been several instances in which the prothrombin determination was of assistance in evaluating the clinical status of patients under consideration for collapse therapy. For example, the patient with hemoptysis in Group 3 (F.G.) was considered for artificial pneumothorax and it was found that his prothrombin had undergone a marked increase following rest in bed and cessation of the hemoptysis. Accordingly stereoscopic Roentgen films were made which revealed closure of the cavity previously seen in the right apex and for this reason collapse was deferred. Because of these considerations it is suggested that the method of prothrombin determination be applied in the study of tuberculous patients particularly when there is a question of cavity closure, activity of the disease or effectiveness of collapse

therapy and when changes in treatment are under consideration. For purposes of investigation the quantitative method appears to be most accurate, but in actual use this may be modified by one of the bedside methods.¹⁰ The Quick method would be simplified if the "lyophilized" thromboplastin becomes available for general use.⁷

Conclusions. 1. Prothrombin determinations are reported on 70 patients with pulmonary tuberculosis.

2. In general, there is an increase in prothrombin in patients in whom the disease is controlled, particularly those with effective collapse therapy. The possible relation of this phenomenon to the destruction of prothrombin which may take place in the lungs is considered.

3. The patients with very active disease show a marked diminution in prothrombin activity, while those with chronic disease of moderate activity or early collapse therapy show a less marked decrease. As clinical improvement occurs, there is a gradual increase in the circulating prothrombin. The possibility of toxic absorption in this connection is discussed.

4. The sedimentation rate of erythrocytes does not always run parallel to the prothrombin level and the variation is not entirely constant. In a general way, however, the prothrombin level appears to give more information concerning the clinical status than the sedimentation rate.

5. The vital capacity bears no definite relation to the prothrombin level, but when the disease is completely inactive there is usually an increase in prothrombin when reduction in the vital capacity occurs.

6. Hemoptysis appears to be associated with a decrease in prothrombin beyond that expected from the stage of advancement of the disease or the toxicity.

7. It is suggested that toxemia may play a part in the diminished prothrombin in patients with active tuberculosis.

8. The inclusion of prothrombin determination in the study of patients with tuberculosis is proposed.

The suggestions and criticism of Drs. Burgess Gordon and L. M. Tocantins are hereby acknowledged.

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THE SURVIVAL TIME AFTER TRANSFUSION OF ERYTHROCYTES OF CITRATED HUMAN BLOOD STORED AT 4° TO 6° CENTIGRADE.

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AN *in vitro* study made in this laboratory² of the keeping properties of chilled citrated human blood showed that the red cells became fragile, and began to hemolyze, near the end of the first week of storage. Clinical observations in which multiple transfusions failed to elevate hemoglobin as expected suggested that these cells were rapidly destroyed in the patients' circulation.

In 1919 Ashby¹ described a method for determining the life of transfused cells. This consists, in brief, of transfusing recipients of blood groups AB, A or B with O blood and making red cell counts with O plasma as diluting fluid. The O plasma clumps the cells of the recipient, leaving those of the donor to be counted as unagglutinated cells. This method, slightly modified, was made use of in the present study. We used a red cell rather than a white cell pipette, as the lower concentration of cells seemed to permit more accurate counting. The 1-hour incubation at 37° C. was omitted, and the storage over night in the refrigerator was effected in the diluting pipette rather than in a test tube into which Ashby blew the blood-plasma mixture. Attempts at more radical modification, especially omission of the period of chilling, gave erratic results. All counts were made in duplicate, 160 small squares being counted for each. Only cells which were completely separated from all others were recorded. The variation between single counts was about 25%, and the average of the two was considered accurate to about 15%, which is the error in ordinary red cell counting.

All individuals have, naturally, some inagglutinable cells. The number varies considerably, being most often under 100,000; but extremes of 215,000 and 10,000 were noted in our studies. This number was determined for each individual immediately prior to transfusion. The difference between this and inagglutinable cell counts made subsequently gave the number of donor cells present in the patient on the various days of observation. Such observations, were, as a rule, made daily, some counts being at longer intervals in cases of prolonged survival. The amount of blood given in most instances was 500 cc.

Investigations were made, all told, on 25 subjects. In 11 of these, because of death, discharge from the hospital, additional trans-

fusions with O blood, or other reasons, studies were not satisfactorily concluded. Individual records of 11 of the 14 completed observations are illustrated in Chart 1. The numbers at the end of the lines represent the days each blood was kept in the refrigerator prior to transfusing it. Observations on the 2-day-old blood were discontinued before the cells had entirely disappeared. Two liberties were taken in transferring the data to the charts. In the case of the 5-day-old blood the count reached 150,000 cells on the 20th day, then remained at this level for approximately 3 months. Since several subjects had inagglutinable counts greater than this prior to transfusion, this record was considered terminated on the 20th day. Likewise the record of the 6-day-old blood showed so little change between the 20th and the 48th days that it was regarded as terminated at the earlier date. This has reduced the scatter of observations on Chart 2, but we feel that the line as drawn more nearly represents the truth of the matter.

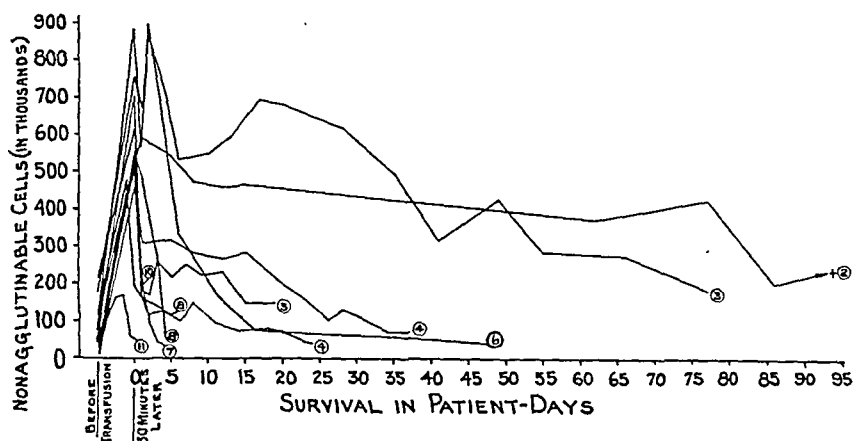


CHART. 1.—Erythrocyte survival after transfusion of stored citrated blood (agglutination method).

Chart 1 tells its own story. There is a sharp rise in the number of inagglutinable cells immediately after transfusion, then a gradual fall as the cells disappear from the circulation. The red cells of the 2- and 3-day-old blood survived as long as did those of fresh blood in Ashby's and Wearn's⁵ studies. As storage time lengthens survival time decreases.

This inverse relationship between storage time and survival time is more clearly shown in Chart 2. This chart is constructed by plotting the number of days during which the bloods were stored against the number of days donors' red cells could be detected in the recipient's circulation. The curve indicates that bloods stored no longer than 2 or 3 days are retained by the recipient, and presumably used by him for long periods. There occurs then a rapid shortening of the survival time of these cells as storage time lengthens.

ens, until, after 7 or more days of storage, the donors' erythrocytes are eliminated in 1 or 2 days.

Additional evidence of rapid destruction of red cells was sought by means of the icterus index and tests for hemoglobin and increase of urobilin in the urine. This was done on 13 of the patients recorded in the charts, and on 21 others. There was, in fact, a moderate increase in blood pigment and in urobilin in some of the instances where old blood was used, and in 2 hemoglobinuria was noted. This correlation, however, was by no means a close one. In this connection it may be mentioned that a higher incidence of jaundice following transfusions of stored rather than of fresh blood has been noted by Fox,⁴ Brewer *et al.*³ and by us.² The absence of jaundice, urobilinuria and hemoglobinuria in some instances of rapid destruction of transfused erythrocytes is probably accounted for by a greater capacity on the part of the endothelial cells and the liver of certain individuals to handle diffused hemoglobin. It is of some importance

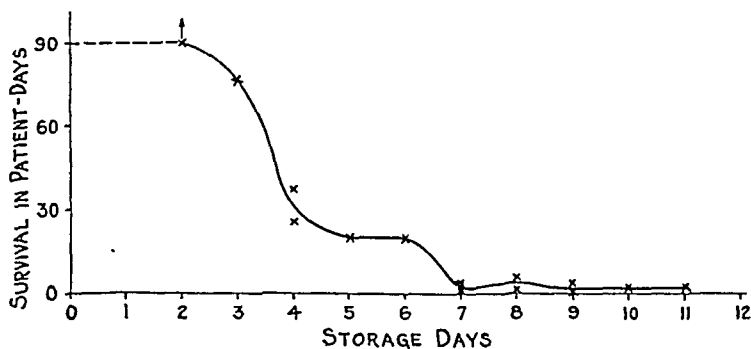


CHART 2.—Relation between storage time and survival of erythrocytes after transfusion.

to appreciate that an absence of the clinical evidences of hemolysis is not proof that hemolysis has not occurred. Failure to appreciate this probably accounts for the numerous expressions in medical literature of satisfaction with "bank" blood, some of it quite old.

Our results with counts of inagglutinable cells are supported by the work of Wiener and Schaefer⁶ who followed the disappearance of transfused erythrocytes with the use of M and N agglutinogens. In their observations the deleterious effect of storage appeared later than in our bloods, prolonged survival being noted up to about the 8th day. After this the curve of shortening intravascular life was similar to ours, but more gradual. The fact that observations were usually made at weekly rather than daily intervals may account in part for this difference.

The demonstration of rapid deterioration of stored citrated blood for transfusion should be of benefit to those interested in "blood banks." The original proponents of this method advocated an upper age limit for stored blood of 14 days. We have used this

limit, and the average storage age of blood in all our 1480 transfusions has been 6 days. We find it unpleasant, now, to realize what relatively worthless material we have been supplying many of our patients in the belief that they were receiving whole blood transfusions.

Conclusion. The erythrocytes of citrated human blood kept at 4° to 6° C. were found to survive in recipients as long as do the cells of fresh blood when storage time did not exceed 2 or 3 days. After this they disappeared with increasing rapidity as storage time increased, until, after 7 or more days in the "bank," their post transfusion survival was in no case longer than 24 or 48 hours.

The authors wish to express appreciation for the coöperation on the part of the Chiefs of the Medical and Surgical Services of this Hospital in making this study possible.

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THE EFFECT OF GLUCOSE IN THE PRESERVATION OF CITRATED HUMAN BLOOD STORED AT 4° TO 6° CENTIGRADE.

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AN *in vitro* study from this laboratory² of the keeping properties of citrated human blood stored at 4° to 6° C. showed the development of visible hemolysis in about 5 days, the rapid disintegration of granulocytes and of platelets, and a speedy decrease in clot forming properties. A subsequent *in vivo* study¹ by Ashby's method of the survival time in the recipient's circulation of red cells which had been stored for varying intervals demonstrated even more convincingly the rapid deterioration of chilled citrated erythrocytes. Up to 2 days of storage transfused cells could be detected in the recipient for 60 to 90 days, a survival period equal to that of fresh blood. Between the 2d and the 7th day the life of these transfused cells shortened rapidly, and after the 6th day all were destroyed by the patient in 24 to 48 hours. Quite clearly such "blood" is an almost worthless medium for whole blood transfusions, except in the largest institutions, where the turnover of the "bank" is complete every 2 or 3 days.

In 1916, Rous and Turner^{8b} demonstrated that glucose greatly

delayed the hemolysis of rabbit erythrocytes stored in the ice-box, and that these cells, up to 2 weeks of storage, served to replace physiologically cells removed from this animal by bleeding. During the preparation of the present paper a number of reports have appeared showing this property of glucose to be effective in the preservation of human cells. Certain considerations, however, need more specific definition, particularly the optimum amount of glucose, and the length of time that such storage will, with certainty, keep blood in a highly usable state.

Methods. Blood from human donors was received into 20% solution of sodium citrate, dihydric, to make a final citrate concentration of 0.4%. The proper amount of glucose was added, gently mixed, and apportioned into 125 ml. Pyrex Erlenmeyer flasks. Flasks were capped with flask hoods and stored at 4° to 6° C. The volume of blood-citrate-glucose was, with one exception noted later, always the same, 30 ml., no matter what the proportions of each, so that the effect of glass contact was the same in all cases. A separate flask was prepared for each day's observation, so that the hemolytic effect of repeated agitation and of repeated warming and chilling was avoided.

Fragility was determined by shaking blood in an electric shaker for 5 minutes and centrifuging to show the color of the plasma, in addition to the usual method with saline dilutions. Hemolysis by inspection consisted of mixing the blood, then centrifuging a portion to show the color of the plasma. Quick's prothrombin time was done by the original method, except of course, that oxalate was not used. The estimation was controlled each day by a parallel determination on a normal blood, and corrected, by simple proportion, to 12 sec. = 100%. The hematocrit used was Wintrobe's; plasma chlorides were determined by the method of Wilson and Ball; phosphates, that of Fish and Subbarrow; potassium, Stahl and Bennett; glucose, Folin and Wu; carbon dioxide combining power, Van Slyke and Cullen, and oxygen capacity by the method of Van Slyke and Stadie.¹⁰

Our first series of observations, in addition to reassessing the preserving properties of glucose, was designed to show the minimum amount of 5.4% (isotonic) glucose which would be highly effective. This was for the obvious desideratum that the volume of fluid for infusion should be as small as possible. In addition, the administration of considerable quantities of glucose would be undesirable in diabetics. The effect on erythrocytes of varying the proportion of blood and glucose, 5.4%, from 2 to 1 to 10 to 1 is shown in Table 1.

It is seen that the larger the proportion of glucose to blood the better the preservation. This is in agreement with the observations of Rous and Turner,^{8a} De Gowin,³ and others. On the other hand, with even so small an amount of glucose as 1 part to 10 of blood, preservation, as compared with that of citrate alone, is clearly superior. The advantage gained by additional amounts of glucose is distinct, but relatively small. With 1 part of glucose to 2 of blood fragility of erythrocytes to saline is essentially unchanged, and hemolysis (shaking) is not present on the 21st day of storage. On the 28th day only slight hemolysis is present. Very probably

somewhat better preservation could be obtained by increasing the proportion of glucose to 1 to 1 or more. We feel, however, that the proportion of 2 parts of blood to 1 of glucose represents a practical adjustment of the 2 considerations; namely, effective preservation, and minimum volume of transfusion material. This technique too avoids the use of excessive quantities of citrate such as was employed by Rous and Turner, the actual amount being 2 gm. per 500 cc. of blood, or per 750 cc. of injection fluid. We have been using blood so stored for some time with complete satisfaction.

TABLE 1.—THE EFFECT OF VARYING PROPORTIONS OF 5.4% GLUCOSE ON THE FRAGILITY AND HEMOLYSIS OF ERYTHROCYTES OF WHOLE CITRATED HUMAN BLOOD KEPT AT 4° TO 6° C.

Proportion of blood to glucose.		Days: 0	7	14	21	28
B 2	{	F.S.	0.40	0.40	0.40	0.45
G 1		H.S.	0.0	0.0	0.0	Tr.
		H.V.	0.0	0.0	0.0	Tr.
B 3	{	F.S.	0.40	0.40	0.40	0.47
G 1		H.S.	0.0	0.0	Tr.	+1.0
		H.V.	0.0	0.0	Tr.	+1.0
B 4	{	F.S.	0.40	0.40	0.40	0.50
G 1		H.S.	0.0	0.0	+1.0	+2.0
		H.V.	0.0	0.0	+1.0	+2.0
B 5	{	F.S.	0.42	0.42	0.45	0.52
G 1		H.S.	0.0	0.0	Tr.	+1.0
		H.V.	0.0	0.0	Tr.	+1.0
B 10	{	F.S.	0.42	0.42	0.45	0.55
G 1		H.S.	0.0	0.0	Tr.	2.0
		H.V.	0.0	0.0	Tr.	1.0

The first three observations were made on the blood of one donor, the last two on that of another donor. F.S. = fragility to saline dilutions; H.S. = hemolysis on shaking; H.V. = visible hemolysis.

In an attempt to secure good preservation in even smaller volume 10.8%, 50%, and crystalline glucose were added to blood in different amounts in 7 experiments. Crystalline glucose produced some hemolysis at once, 50% glucose at the end of 7 days. The 10.8% glucose delayed hemolysis until the 28th day in one experiment, the 21st in another. With it, however, red cells swelled more, and plasma chloride decreased more sharply than with 5.4% glucose. Because of these observations isotonic glucose only was regarded as suitable for blood preservation.

Three observations were made with citrate-glucose-saline mixture, one with twice isotonic fluid (glucose 5.4%, saline 0.9%) and two with isotonic fluid. Hemolysis appeared on the 21st day in the first instance, on the 14th day in the other two.

Two observations only were made on the effect of anerobic storage, in both of which hemolysis appeared 7 days earlier than in controls.

This is contrary to the findings of De Gowin³ and others. However, the technical difficulties involved in producing anerobic conditions and our satisfactory results under aerobic conditions removed our interest from further pursuit of this possibility.

TABLE 2.—THE COMPARATIVE KEEPING QUALITIES OF A SPECIMEN OF HUMAN BLOOD IN CITRATE, 0.4%, AND IN CITRATE-GLUCOSE AT 4° TO 6° C.

DAY:	CITRATED BLOOD.								CITRATED BLOOD, 2 PARTS; GLUCOSE 5.4%, 1 PART.									
	0	1	2	3	4	6	7	14	0	1	2	3	4	6	7	14	21	28
Granulocytes . . .	30	28	28	26	18	14	10	?	21	20	20	21	21	19	16	4	1	?
Platelets . . .	145	115	92	86	56	43	49	28	96	92	89	82	69	59	63	46	40	23
Prothrombin time . .	12	12	13	13	14	14	15	18	17	17	17	17	18	16	18	22	25	31
Isoagglutinin . . .	32	32	8	16	16	16	16	16
False agglutination .	0	0	0	0	0	0	0	0
Hemoglobin . . .	14	14	14	10.5	10	10	10
Oxygen capacity . . .	16	16	17	12	13	14	13	13
Fragility NaCl . . .	40	40	425	425	425	475	475	85	40	40	40	40	40	425	425	425	45	50
Hemolysis shaking . .	0	+2	+3	0	0	0	0	+1
Hemolysis visible . .	0	+1	+2	0	0	0	0	0
Hematocrit . . .	39	40	40	33	33	34	33	34
Chloride plasma . . .	578	570	572	392	390	..	368
Phosphate inorganic .	4	7	10	3	3	..	5
Potassium . . .	16	78	..	11	72
Glucose . . .	85	20	18	1820	1810	1700	1590	1560
CO ₂ plasma . . .	47	21	14	37	11	1	1	?
Suspensibility . . .	G	G	G	G	G	G	G	G
Culture . . .	S	S	S	S	S	S	S	S

Granulocytes in hundreds; platelets in thousands per c.mm.; prothrombin time in seconds; isoagglutinin in dilution titer; hemoglobin in gm. per 100 cc.; oxygen capacity in vols. %; fragility NaCl in salt concentrations (40 = 0.4%); hematocrit as % of packed red blood cells; plasma chloride, inorganic phosphate, potassium, glucose, in mg. per 100 cc.; CO₂ plasma as vols. %; G = good, S = sterile. Fractions omitted.

The majority of those using glucose advocate bleeding donors directly into a citrate-glucose mixture. This has two disadvantages: first, glucose is apt to caramelize when sterilized with citrate; second, when a measured amount of preservative is placed in the reception flask prior to bleeding the proportions of blood and glucose will not always be the same because of the occasional failure to secure the amount of blood desired. For these reasons we prefer to add glucose after the blood has been collected. This is done by pouring in half as much glucose as blood, using the graduations on the bottle to measure by. The fluids are then mixed gently with a sterile glass rod. Quantitative determinations of top, middle and bottom portions of the fluid in six instances showed diffusion of glucose to be uniform throughout.

A second consideration connected with the practice of adding glucose after bleeding was the possible effect of delay in so doing. This was observed on a single blood divided into 5 equal parts. To 1 of these glucose was added at once and to the others after intervals of 6, 12, 24 and 48 hours. Hemolysis (shaking) appeared on the 20th day in the first 3 samples, in 5 days in the latter 2. We have assumed, consequently, that a 12-hour delay in adding glucose

in the case of an occasional specimen collected out of usual hours is permissible, though not ideal.

The ease with which blood and glucose might become infected has been studied by cultures of 100 specimens collected in routine fashion. All have been sterile.

Table 2 gives in detail a final comparative study of equal parts of blood from one donor received into 20% citrate to make a final concentration of 0.4%. To one part a half portion of 5.4% glucose was added. The only departure from the storage technique described above was that samples for the observations on the 2d to the 6th day inclusive were placed in test tubes.

Although the chief interest in this and similar studies has been the preservation of erythrocytes, from the standpoint of practical transfusion alterations in other elements of whole blood are of comparable importance. These studies were designed to include as many observations as practically possible, omitting, however, consideration of the antibacterial and immunological properties, which have been studied by Kolmer,^{4a,b} and possible alterations of plasma.⁵ In drawing conclusions use is made of chemical data, observations on white cells, platelets, and so on, similar to those in Table 2, but omitted for brevity. Such studies formed a part of all of 20 experiments on the various conditions of blood storage discussed above.

Loss of granular cells, platelets and prothrombin takes place perhaps a little more slowly in glucose, though the difference is slight when other of our experiments are examined. Howell's prothrombin time was done in 6 studies with varying amounts of 5.4% glucose and was found to increase only a little less rapidly than in citrate studies.² This depreciation in elements essential for the formation of clot seems sufficiently rapid to contraindicate the use of stored blood, even with glucose, in any of the hemorrhagic diathesis. The effect of granulocyte loss on transfusion in sepsis has been commented on by Kolmer. Isoagglutinins and isoagglutinogens were studied to be sure that storage would not interfere with accurate typing and cross agglutination. In none of the 8 experiments was there any loss of specific agglutinability, nor the development of abnormal agglutinating tendencies. Agglutinin titre was preserved a little better in glucose.

Hemoglobin, red cell numbers (counted on each day of observation, but omitted from table) and oxygen capacity remained essentially unchanged under all conditions. The most clear cut effect of glucose was to delay the development of definite erythrocyte fragility as shown by saline dilutions, from about the 6th day in citrate to the 21st day or 28th day. Hemolysis on shaking appears an interval later in Table 2, but in other observations the two changes were approximately simultaneous. It should be noted that the test for hemolysis by inspection, that is after mixing the cells and plasma

and centrifuging, is less sensitive than by shaking; and that inspection of the supernatant plasma is even cruder. Consequently the appearance of hemolysis in any specimen of stored blood shows that it is unfit for use. The idea that a little hemolysis makes no difference must be abandoned along with the concept that it is hemolyzed blood itself which is objectionable. Hemolyzed blood, certainly in moderate amounts, is harmless on intravenous injection. The importance of erythrocytolysis in stored blood is the indication it furnishes that the cells have already undergone such changes as to render them incapable of physiological function.

Other evidences of red cell changes are furnished. The hematocrit readings in Table 2 show no alteration in cell size. In other observations, however, especially in hypertonic solutions of glucose, swelling took place, and in general an increase in size of stored erythrocytes appeared to be correlated with hemolysis. Roughly parallel to cell swelling is decrease in plasma chloride, which, it appears, enters the cells. The loss in some instances was as great as 80 to 90 mg. per 100 cc. in 28 days. A shift of ions in the opposite direction is illustrated by the increase in inorganic phosphates and of potassium in the plasma. The retardation of the shift of ions by glucose is well shown. De Gowin and Scudder,⁹ however, found potassium to diffuse at about the same rate in glucose as in citrate solution, in both being rather more rapid during the first period of storage than later. Glycolysis and a fall in carbon dioxide combining power is more rapid in bloods to which glucose has been added. This apparent inconsistency may be explained on the supposition that a slight change in the direction of acidity would delay hemolysis. These chemical changes have been discussed by Peters⁷ and by Maizels and Whitaker.^{6a,b}

These several evidences of alteration in the cellular element and in the clot promoting properties of stored blood were consistently present, and progressed steadily, differing only in that their development was less rapid under the more favorable conditions. Similar observations have been made by others, all of whom are in substantial agreement.

It is of some importance to note a difference in the keeping properties of blood from different donors under identical conditions. This, of course, has been a common observation with chilled citrated blood. It might be attributed to technical errors, such as too vigorous shaking, delay in chilling, and so on. In these experiments, however, technical details were carefully controlled, and so we are inclined to assign as the major cause of such differences variations inherent in the blood of different individuals. In any case this shows the wisdom of allowing a generous margin of safety in setting an upper age limit for stored blood. To us, 14 days seems reasonable, although in our best experiments no hemolysis was apparent at the 21st day. In support of this it was recalled that Rous and

Turner found rabbit erythrocytes physiologically active up to the 14th day, not so on the 21st, although hemolysis had not occurred.

Conclusions. Glucose (5.4%) prevents the hemolysis of erythrocytes of whole citrated human blood kept at 4° to 6° C., for 3 to 4 weeks. With citrate alone hemolysis appears near the end of the 1st week.

This preserving effect is less marked on granulocytes, platelets and on the clot-forming properties.

One part of isotonic glucose to two parts of blood is effective, and has the advantage of not increasing too greatly the amount of fluid to be injected.

It must not be thought that blood preserved by chilling and the addition of glucose remains in a state of hibernation, or suspended animation. The processes of decay go on steadily, being only retarded by the favorable environment. There is, therefore, a strict limit to the time that blood for transfusion may properly be stored. This limit is shorter than generally supposed because of the fact that these red blood cells become incapable of substituting for the cells of the recipient prior to suffering any hemolysis.

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LEUKEMOID REACTIONS.

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BLOOD pictures simulating leukemia have been recognized as unusual reactions in rare non-leukemic conditions for several years. Since the introduction of chemotherapeutic agents of the sulfanilamide group, however, leukemoid reactions of varying grades of severity have become sufficiently common to arouse general interest

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in the differential diagnosis of all conditions giving this type of blood picture.

The leukemoid reactions which result from therapeutic measures are more of a puzzle in confusing the prognostic interpretation of the differential count than as a diagnostic problem. However, a large number of other clinical conditions simulating leukemia may present great difficulties in diagnosis. Most numerous and diverse are the group of disease states which are capable of producing a myeloid type of reaction in the blood. We have found it particularly helpful in this type of blood picture to employ a classification based on causative mechanisms, evolved as a result of the study of many such cases at Baylor Hospital, involving as they did a heterogenous and widely diverse group of diseases and clinical conditions.

This classification has been of help, first of all, in suggesting the many abnormalities other than leukemia which must be considered with wide deviations of the blood picture from normal. In addition, diagnosis and differentiation from leukemia has been simplified due to the systematic arrangement of leukemoid reactions according to apparent causal mechanisms.

A rather voluminous literature concerning the probable causes of leukemoid blood pictures has accumulated, but relatively little has been attempted in classification. Krumbhaar¹⁰ first applied the term "leukemoid" to blood pictures simulating leukemia and divided these reactions into the main groups, namely: (1) those presenting a real difficulty in diagnosis from leukemia and (2) those having hematologic similarity alone. Later Fitz-Hugh⁶ classified these leukemia-like conditions according to their blood picture into myeloid, lymphatic, and monocytic types. He also commented on the difficulty of defining these groups of reactions, since leukemia itself exhibits such a variety of manifestations, even including a low count. Schilling¹⁶ included direct bone marrow irritations as well as the non-leukemic myeloses under the heading of liberating leukocytoses, thus making no effort to separate these conditions on an etiologic basis.

In order to restrict the type of conditions under consideration here to those which actually simulate leukemia closely enough to be a diagnostic problem, we have adopted an arbitrary definition of the leukemoid picture in the selection of cases for this report. We considered as leukemoid any reactions in which the following were found: (a) Total leukocyte count over 50,000; (b) presence of immature cells of the "blast" stage; or (c) a combination of both (a) and (b).

The cause of leukemoid reactions has not been satisfactorily explained, although many conditions have been named which at times may result in such reactions, but which usually do not. For example, Heck⁷ collected from the literature 16 clinical conditions which have been responsible for this type of blood picture.

CLASSIFICATION OF LEUKEMOID REACTIONS OF MYELOID TYPE
ACCORDING TO APPARENT CAUSATIVE MECHANISM.

- I. *Bone marrow irritation or stimulation:* This may be physical, chemical, or allergic in character.
 - A. General features of blood picture.
 1. High leukocyte count, often over 75,000.
 2. Eosinophilia and basophilia frequently prominent.
 3. Degree of leukocyte immaturity less marked than in II and III, usual myelocytes with few or no myeloblasts.
 - B. Conditions or diseases capable of producing this type of reaction.
 1. Osteomyelitis and complicated bone fractures.
 2. Metastatic carcinoma of bones.
 3. Chronic infectious granulomata of bone.
 4. Hodgkin's disease with bone marrow lesions.
 5. Severe reactions to intravenous medication.
 6. Severe reactions following transfusions.
 7. Pyogenic infections.
- II. *Liberation leukocytosis:* Marrow response to overwhelming demand.
 - A. General features of blood picture.
 1. Leukocyte count variable, usually less than in Group I.
 2. No definite eosinophilia in most cases.
 3. Degree of leukocyte immaturity generally greater than Group I.
 - B. Conditions or diseases capable of producing this type of reaction.
 1. Acute hemolysis in:
 - a. Sulfanilamide therapy (and related drugs).
 - b. Familial hemolytic anemia.
 - c. Blackwater fever of malaria.
 - d. Sick cell anemia.
 - e. Hemolytic poisons, phenylhydrazine, and so forth.
 2. Erythroblastic anemia.
 3. Pernicious anemia in crisis.
 4. Following severe hemorrhage.
 5. Recovery phase of granulocytopenia.
 6. Polycythemia, especially in anemic phase such as following therapy.
 7. Septicemia.
 8. Stage of impending death in acute infections.
- III. *Ectopic hematopoiesis:* Formation of blood producing foci outside of bones usually due to destruction or crowding of bone marrow.
 - A. General features of blood picture.
 1. Leukocyte count relatively lower, often in normal range.
 2. Eosinophilia not prominent.
 3. Degree of leukocyte immaturity more marked than in Groups I and II.
 - B. Conditions or diseases capable of producing this type of reaction.
 1. Osteosclerosis and osteofibrosis.
 2. Prolonged increased demand in:
 - a. Chronic form of familial hemolytic anemia.
 - b. Prolonged untreated pernicious anemia.
 3. Tumors with extensive replacement of bone marrow.
 4. Lipoid histiocytosis.

Tuberculosis has been most frequently given as a cause of leukemoid pictures, as the reports of Marzullo and deVeer,¹³ Leibowitz,¹² Custer and Crocker³ and others indicate. The relation of true

leukemia and tuberculosis has been a cause of confusion. Undoubtedly leukemia may cause breakdown and activation of tuberculous lesions, but, on the other hand, tuberculosis may in rare cases tend to suppress leukemic findings in the blood as Jaffe's⁹ cases clearly demonstrate. Most illuminating is the work of Stasney and Feldman,¹⁷ which showed a leukemoid reaction upon administration of tuberculin to previously sensitized animals.

Septic infections may simulate leukemia, either as an extremely active response of the marrow or more particularly, when the infection is directly in the marrow, as pointed out by Schilling.¹⁶ Arneith² suggests a selective septic effect on one type of cell as the causative mechanism in pyogenic infections.

Carcinoma has frequently been reported as causing a leukemoid picture. Ercklentz,⁴ and Kugelmeier¹¹ believe a toxic factor in carcinoma acts on the marrow. Muller and Werthemann¹⁴ liken the tumor products to a parenteral injection of protein producing leukocytosis. Reich¹⁵ assumes that a direct irritation due to metastatic carcinoma produces hyperplasia and leukocytosis.

Atypical blood pictures with osteosclerosis have frequently been confused with aleukemic myeloid leukemias because of the low count, and the extramedullary foci of hematopoiesis found in various organs. Anagnostu¹ points out that these reactions are compensatory responses to mechanical displacement of bone marrow. Stephens and Bredeck¹⁸ also point out the primary rôle of the bone changes and the relationship of their severity to the blood picture. A similar displacement mechanism may be seen in the case of Niemann-Pick's disease described by Fisher.⁵

Many other conditions, apparently unrelated to each other have been reported as giving leukemoid reactions in rare or solitary cases. We believe, however, that most of these can be classified in respect to the mechanism by which blood formation is disturbed and the leukemoid blood picture produced.

Differentiation From Leukemia. The actual diagnosis and differentiation of any given case from true leukemia may be very difficult, but several practical points can be used. First, recognition of any of the clinical conditions capable of producing a leukemoid reaction should throw doubt on the additional diagnosis of true leukemia on the basis of a suggestive blood picture only. Of course, it must be understood that even the conditions listed need not produce a leukemoid picture constantly. In fact, in most of these leukemoid reactions are very much the exception. Second, useful differential features, and often definite criteria, can be made out by the hematologist in study of the blood smear. Finally, the finding from simple laboratory tests such as platelet count and hemoglobin may be helpful. The laboratory differentiation can be given in tabular form.

Leukemoid Picture.

1. Immature as well as mature leukocytes show normal morphology.
2. Myeloblasts may be present but usually are under 10%.
3. Immature red cells (normoblasts and erythroblasts) often increased in proportion to leukocyte immaturity.
4. Platelets usually normal or increased, may be moderately decreased in Group 3.
5. Anemia variable depending on causal factors.

True Leukemia.

1. Leukocytes are atypical, particularly the immature ones.
2. Myeloblasts may be numerous, as high as 99+ %.
3. Immature red cells rarely increased in proportion to leukocyte immaturity.
4. Platelets decreased, often severely, may be increased in chronic myelogenous form only.
5. Steadily progressing anemia becoming extreme.

Our largest group of cases were those classified as bone marrow irritations. Of course, not all of these cases were completely clear cut, particularly in carcinoma with marrow metastasis where some marrow destruction and ectopic blood formation are seen as is illustrated in our first case. Case 2 is representative of osteomyelitis with marrow irritation. Typical of Hodgkin's disease with bone marrow lesions, Case 3 very closely simulates leukemia in its clinical picture, but is easily differentiated by biopsy. Case 4, remarkable for its exceedingly high count, apparently can be explained as a pyogenic infection with a selective septic irritating effect on marrow cells.

CASE 1.—R. L. P., white female, aged 51, admitted with complaints of shortness of breath and blue spots on legs and arms for 2 weeks prior to admission. *Past history:* small mass in left breast, 1 year without apparent increase in size, loss of 95 pounds in 7 months.

Physical examination shows subcutaneous hemorrhages over legs, hips, and arms; heart slightly enlarged to left, rate rapid, rhythm regular; liver 4 fingers below costal margin. A small mass in left breast unattached to skin, size of walnut, was found.

Laboratory examinations: leukocytosis, fairly severe anemia, no definite depression of platelets and definite immaturity of leukocytes.

July 18, 1940. Red count, 2,520,000; leukocytes, 25,500; differential: 1 eosinophil, 1 basophil, 6 myeloblasts, 16 myelocytes, 18 young forms, 40 band forms, 3 segmented forms, 13 lymphocytes, and 3 monocytes.

July 20, 1940. Platelets, 210,000; leukocytes, 35,000; with large number of myelocytes, myeloblasts and pre-myeloblasts; also many erythroblasts.

Postmortem diagnosis: carcinoma of breast with tumor thrombi and hemorrhages, in breast, bone marrow, lung, liver, spleen and suprarenal. Small ectopic foci of hematopoiesis in liver, spleen and lymph node.

CASE 2.—J. S., negro male, aged 40, entered the hospital complaining of low back pains for 3 months, and pain and difficulty in using the lower extremities for 2 months. This patient had been seen previously in the antiluetic clinic as early as 3 years ago, and at that time the leukocyte count was 23,000, with a differential showing 87% neutrophils with 13% lymphocytes. Over this 3-year period he had had several blood examinations, the leukocyte count varying from 23,000 to 66,000 with differential count showing 2% to 3% myeloblasts, 15% to 20% myelocytes, 20% to 40% eosinophils, 2% to 4% basophils, 7% to 13% lymphocytes, the remainder being neutrophils. At the time of admission he presented the picture of a slightly undernourished, slightly emaciated negro male, with

skin and mucous membranes pale. The heart and lungs appear normal, the abdomen showed 3+ tenderness and voluntary rigidity of the lower portion. Liver, spleen and kidneys were not palpable. Rectal examination revealed a firm prostate of normal size.

Laboratory examinations: total white count of 78,400, with a differential reading: eosinophils, 18%; basophils, 5%; myelocytes, 20%; band forms, 30%; segmented forms, 25%; lymphocytes, 2%. Red cells, 2,800,000 with 44% hemoglobin. Wassermann, Kahn and Kline tests were negative. Stool examinations for parasites were also negative. Spinal fluid: Wassermann test was negative, colloidal gold curve was negative, cell count was 4. Roentgen ray examinations were negative except for an unexplained shadow in the region of the right hip.

Clinical course: the patient continued to complain of pain in his back, abdomen and right side. He ran a sustained temperature of 101° to 102°; pulse, 120 to 130. Patient rapidly became weaker and died on the 34th hospital day.

Autopsy: chronic suppurative osteomyelitis of the sacrum; extensive gangrenous necrotic abscesses of right thigh and right side of the pelvis; abscess of the posterior lobe of the right lung; extensive suppurative bronchopneumonia of the posterior portion of the right and left lungs.

CASE 3.—J. F., white male, aged 23, entered the hospital complaining of general malaise, fever, slight cough, and enlargement of the glands of the neck and groin for 4 months.

Physical examination revealed a rather well-developed but slightly undernourished and anemic-looking white male, not acutely ill. The neck showed extreme enlargement of the anterior and posterior cervical lymph glands and supraclavicular glands. These lymph nodes were discrete and movable but not tender. A similar type of glandular enlargement was noted in the axillæ and inguinal regions. The heart and lungs appeared normal and the spleen was palpable.

Laboratory examinations: red blood count 3,160,000 with 70% hemoglobin. White blood count 54,350 with the differential showing basophils 2, eosinophils 32, lymphocytes 10, neutrophils 55. Platelet count was 201,600. Wassermann test was negative. White blood count ran from 45,500 to 62,000 with 54 to 55 neutrophils, 25 to 31 eosinophils, 5 to 20 lymphocytes. Later admission to the hospital showed the lymph glands to be slightly larger. The patient also developed a rather severe diarrhea 6 months after the first admission. At this time the laboratory work showed a platelet count of 54,000. Red count 3,500,000 with 55% hemoglobin. White blood cells 50,250 with 48 eosinophils, 43 neutrophils, 4 lymphocytes, and 5 degenerative or unidentified cells. Reticulocytes, 1.2%. On one occasion at this time a few myelocytes were also seen. The patient became progressively worse and expired.

Autopsy: marked generalized Hodgkin's disease of lungs, liver, spleen, lymph glands and adrenals with numerous Hodgkin's lesions in the bone marrow.

CASE 4.—M. M., a colored female, aged 24, entered the hospital in a comatose condition. Her chief complaints were a painful rectum and sore mouth for 3 days. On physical examination a draining ischio-rectal fossa abscess was found. Patient was acutely ill with temperature 102°, pulse 125, and respiration 29.

Laboratory examinations: initial blood count of 206,000 with a differential showing basophils 5, young forms 27, band forms 20, segmented forms, 38, lymphocytes 10. Later counts varied from 168,750 to 25,000 and showed a differential with from 1% to 2% myeloblasts, 7% to 13% myelocytes. Seven days from admission the count was 10,000 with a normal differential and remained so until time of dismissal.

Although the liberation leukocytoeses do not constitute the largest groups in our series, it is probable that the most common leukemoid picture seen today will belong in this group. Case 5 of this group, with hemolytic anemia from sulfanilamide, is typical of this reaction. Cases 6 and 7 closely resemble each other with a mixture of young cells of lymphatic and granular types. In these 2 cases the myeloid response of the pyogenic infection seems to be heightened in some peculiar way by the earlier pertussis with its lymphocytosis. Also, the height of the leukocyte count is due in large measure to the absolute increase of lymphocytes. In familial hemolytic anemia, the blood picture may be hematologically identical to that induced by sulfanilamide and its related compounds. No case of hemolytic anemia is included here since in studying this disease, none of our series met the criteria set up in this paper. However, 1 case was seen with a high proportion of myelocytes and a leukocyte count of 40,000.

CASE 5.—G. V. S., white female, aged about 30, was admitted to the hospital by way of the emergency room. She had been in a severe automobile accident, and was unconscious. An examination at that time revealed a fracture of the basal portion of the skull, a fracture of the right femur and numerous bruises and lacerations over the entire body. Her condition was very critical and she remained essentially the same until the 8th hospital day, at which time she developed a streptococcic meningitis. Sulfanilamide (120 grains) was given intravenously for 3 days and later, sulfanilamide (15 grains) was given orally every 4 hours, and then in decreasing doses.

Laboratory examinations: on admission the white count was 16,300 with a left shift present. Red count was 3,420,000 and hemoglobin 71%. After the development of meningitis and the first dose of sulfanilamide, the total white count was 53,700 with the differential showing 3 myelocytes, 2 young forms, 26 band forms, 50 segmented forms, 17 lymphocytes, 2 monocytes, 5 erythroblasts and 23 normoblasts, per 100 white cells. Sulfanilamide was discontinued on the 19th hospital day and 5 days later the blood smear showed a total white count of 9500 with no abnormal cells present in the blood smears examined. At the time the intravenous sulfanilamide was given, her sulfanilamide concentration was 9.4 mg. per 100 cc. This concentration varied from 7 to 30 mg. per 100 cc. over the 11-day period, during which she was receiving the drug. During this time the red cells dropped to 2,450,000 and numerous small repeated blood transfusions were given. The reticulocyte count showed a 12% response.

The patient improved and was discharged after a lengthy stay in the hospital. Later blood smears showed no abnormal cells.

CASE 6.—D. H., aged 2½ years, was admitted to the hospital with a clinical diagnosis of whooping cough. During the course of his stay the child later developed lobar pneumonia. The total white count at that time was 52,875; differential: 1 myelocyte, 16 young forms, 24 band forms, 9 segmented forms, 43 lymphocytes, 6 monocytes, and 1 lymphoblast. Two nucleated red cells were also seen per 100 white cells examined.

The patient improved and was discharged at a later date. No abnormal cells were found at other examinations.

CASE 7.—This case is similar to Case 5. A 5-year-old child was admitted to the hospital with a clinical case of empyema following an attack of pneumonia. At that time the white count was 103,000 with a severe left

shift present. Many myelocytes and about 50% lymphocytes were found on the differential count.

The patient improved and the count returned to normal at the time of discharge.

The most interesting group of our classification is made up of those leukemoid reactions associated with ectopic blood formation. This is apparently due either to actual physical reduction of bone marrow volume below the amount necessary to maintain normal blood cell values or to a chronic excessive demand which the normal marrow is incapable of supplying alone. Case 8 illustrates the first mechanism, Case 9 the second.

CASE 8.—B. H., a colored female, aged 46, entered the hospital complaining of weakness, swelling of the abdomen, dyspnea, dependent edema and loss of weight for 8 months. The present illness had an insidious onset with the symptoms gradually progressing and increasing in intensity to the time of admission.

Physical examination revealed an emaciated colored female, markedly dyspneic and orthopneic, appearing acutely ill. The skin and mucous membranes were markedly pale, the chest showed moist râles along both bases of the lung. The heart was enlarged to the left. Apex impulse in the sixth interspace 3 inches from the midline. The liver was enlarged, being palpated 10 cm. below the costal margin in the midclavicular line. The spleen was also palpable and enlarged and abdominal fluid was demonstrable. The vaginal examination revealed a nodular enlarged uterus which was also palpated from the exterior. Dependent pitting edema of the extremities was seen.

Laboratory examinations showed the Kline test to be 4+, red blood count 1,720,000, with 17% hemoglobin. White count was 10,500 with a differential showing 2 basophils, 16 band forms, 8 young forms, 27 segmented forms, 8 lymphocytes, 6 myelocytes, 2 micromyeloblasts, 27 myeloblasts, 1 erythroblast, and 1 normoblast. Platelet count was 101,000. A sternal puncture was attempted, but the operator experienced great difficulty in obtaining a specimen. In fact, it is stated that no actual marrow was obtained, and a differential count made on the fluid obtained at the sternal puncture revealed essentially the same as that of a blood smear. The patient's condition was very critical and she expired on the second hospital day.

Autopsy: osteosclerosis with ectopic hematopoiesis of the lungs, liver, spleen, kidney and lymph glands.

CASE 9.—J. B. A., white male, aged 60, was known to have been always somewhat pale, and to have had splenomegaly at 10 or 12, and at 25 years of age. Since the age of 25, he has had intermittent attacks of splenomegaly, usually lasting a month or so with associated loss of 10 to 20 pounds. During these times there have been no particular symptoms other than awareness of splenic tumor and some slight tenderness in the RUQ. Since 1933 the patient has been treated occasionally by Roentgen ray therapy. During the past 10 years attacks have been more frequent and severe and of longer duration. Record shows 2 attacks of jaundice in youth.

Gastro-intestinal complaints, particularly pertaining to gaseous indigestion, have been voiced for many years. In addition, the following complaints are listed, which have no direct connection with the illness as stated above: habitual constipation; pyorrhea, necessitating removal of all teeth; appendectomy at about 30; repair of postoperative hernia at 50, with release of an adhesion near the spleen at that time; rheumatic pains in elbows, knees, and calves of legs, increasingly worse; visual complaints for a period of many years, apparently with no correlated organic finding.

The electrocardiogram shows frequent ventricular premature contractions; left axis deviation, otherwise negative.

Laboratory examinations: red blood count, 4,500,000; icterus index, 10; reticulocytes, 11%. The fragility was increased but occasionally approached normal. The red corpuscles were of small diameter and thicker than normal. Leukocytes ranged from normal to 15,000 per c.mm.; in one hemolytic episode they were as high as 73,500. There were some immature leukocytes at all times, but they became very numerous when the leukocyte count was high. Even when the counts were within the normal range myelocytes and myeloblasts were constantly present. The differential count in the worst episode with the leukocyte count, 73,500, was as follows: 2 basophils, 1 eosinophil, 5 myeloblasts, 9 myelocytes, 34 young forms, 40 band forms, 4 segmented forms, 5 lymphocytes. At all times the immature leukocytes were perfectly regular and typical in every respect. Usually a variable number of immature red cells were present, including normoblasts, erythroblasts and rare megaloblasts.

Discussion. The cases reported in this paper illustrate the many varieties of disease states which may give leukemoid reactions. They also indicate wide differences in the ease or difficulty of diagnosis as represented by the reaction of sulfanilamide and the unusual case of osteosclerosis. Despite the very close similarity of some of these blood pictures to leukemia, we believe it is essential to recognize the fundamental dissimilarity of the basic pathologic changes. In leukemia there is an unrestrained proliferation of a primary nature of abnormal immature leukocytes in normal (bone marrow) and abnormal (other organs and tissues) locations. In leukemoid states there may be proliferations secondary to other causes of normal immature leukocytes in abnormal locations. These proliferations called ectopic hematopoiesis are limited, according to the need for such cells in the blood, and unlike the proliferations in leukemia do not overgrow and encroach upon normal tissues with serious impairment of organ function. Another point of difference is that all the myeloid elements are found in the ectopic foci of leukemoid reactions. Not only are myelocytes and myeloblasts found, but also erythroblasts and megakaryocytes.

The leukocyte count which is one of the chief points of similarity between leukemoid states and true leukemia is not one of the essential characteristics of leukemia. On the contrary, the count in leukemia may be lower than normal. The number of leukocytes in the blood seems to be related to the level of maturation of the immature cells proliferating in the tissues, as pointed out by one of us⁸ in an earlier paper. Of course, leukemoid reactions may also show low counts, and in these cases we find the greatest immaturity of leukocytes and greatest difficulty in diagnosis. However, in the leukemoid case the immature cells are abnormal only in their lack of maturity. They do not show the atypical features of leukemic cells such as abnormal lobulation, indentations or clefts of nuclei, or unusual granulations such as Auer rods. Another important abnormality of leukemic cells which we have not seen in leukemoid

reactions is the lack of correlation between the apparent age of the nucleus and the age of the cytoplasm. Such morphologic differences in the cell are important to the hematologist and may in rare cases be the chief and distinguishing feature.

The most extreme example of leukocyte immaturity in our series was Case 8. In this case, due to virtual elimination of all bone marrow by sclerosis, ectopic foci carried on practically all the blood formation. To make things worse a large portion of this ectopic myeloid tissue in lymph nodes was destroyed by tuberculous lymphadenitis. The extreme demand apparently resulted in the proliferation and release of cells which we believe to be even more immature than myeloblasts, corresponding to the primitive free cell of Sabin.

While classification of leukemoid reactions according to their general mechanism of causation as herein proposed is easily done in most instances, it is difficult or impossible to determine the exact abnormalities of leukocyte proliferation, maturation or release responsible for the blood pictures of these cases. Under our first group of marrow irritation, little can be said concerning the stimulation of proliferation or maturation responsible for very high counts since the factors influencing these processes are not well understood. In some cases there seems to be an unusual response to substances produced in pyogenic infections, while in others there is some obscure relationship to the effect of location of lesions actually in the bone marrow.

Normally, the leukocyte release mechanism seems to depend on the fact that active motility is found only in the relatively mature cells. To get into the blood stream from their extravascular point of origin, these leukocytes pass through the endothelium of the marrow capillaries and sinuses by ameboid movement. In our first classification two possible factors may be assumed, the one very active proliferation, the other damage and even actual breaks in the vascular endothelium of the marrow. Could it be that this combination of growth pressures together with capillary and sinus damage permits the immature non-motile cells to be washed into the blood stream? That such damage to vessels may occur is demonstrated in Case 1, where tumor thrombi and hemorrhages were found in the bone marrow. With liberation pictures, the release of immature cells is even more obscure in its mode of operation. Here again, however, injury to the endothelium by toxins, anoxemia or chemical poisons may be a factor. In the case of ectopic hematopoiesis, normal control of leukocyte release is lost because of the abnormal location of blood cell formation. In these ectopic foci, such as in the spleen or liver, hematopoiesis is not necessarily extravascular and as a consequence, immature cells may easily be washed into the circulating blood.

Conclusions. 1. A classification of leukemoid reactions of myeloid type is presented.

2. Cases illustrating this classification are reported.
3. Differentiation of the leukemoid picture from leukemia is discussed.

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ATRIOVENTRICULAR NODAL RHYTHM.

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THE extensive use of the electrocardiograph has served to emphasize the importance of abnormalities in the rate and rhythm of the heart. Such a cardiac disturbance requiring careful interpretation is atrioventricular nodal rhythm, in which the auriculoventricular node assumes the rhythmicity of the heart independently of the sino-auricular node. Three conditions are necessary for the establishment, even for a short time, of atrioventricular rhythm: 1, marked depression of the normal pacemaker of the heart and failure of any other part of the auricular muscle to assume this rôle; 2, normal activity (potential or latent ordinarily) of the pacemaking function of the auriculoventricular node; and, 3, ability of the impulse to pass backward from the junctional tissue into the auricles to cause their contraction, that is, an absence of a state of reversed block.^{13a} During the time that the *A-V* node is acting as pacemaker the auricles respond to impulses from below, the ventricles to impulses from above.¹

In the literature to date 50 cases of nodal rhythm, due to a variety of causes, have been reported. It has been observed in apparently normal hearts,¹⁴ following auricular flutter,^{13b} due to atropine,¹⁵ digitalis,¹² subacute bacterial endocarditis,⁵ coronary thrombosis,^{9,11} scarlet fever,⁶ quinidine sulphate,⁸ active rheumatic fever,³ anesthesia,¹⁰ sulphanilamide,⁴ and essential hypertension.⁷

Clinically, certain cardiac features may be present but none are

distinctive of nodal rhythm. The heart rate may be normal (60 to 99), slow (30 to 59—nodal bradycardia), or rapid (100 to 160—nodal tachycardia). Marked palpitation may be a major complaint as a result of the simultaneous contraction of the auricles and ventricles.¹⁵ Unduly large impulses in the jugular vein due to the synchronous contraction may also be present.²

The diagnosis of atrioventricular nodal rhythm, however, can be made with certainty only by means of the electrocardiogram. In the electrocardiogram it is indicated by the *P* wave, usually inverted, falling within or just after the *QRS* complex. The ventricular complex is normal in form. Even the electrocardiogram can and does offer some difficulty in interpretation due to the simultaneous presence of other changes in the tracing. Nodal rhythm may be confused with auricular fibrillation with complete heart block, especially if in the nodal rhythm the *P* wave is buried in the *QRS* complex and nodal bradycardia is present. Here the absence of jugular pulsation in fibrillation and the presence of unduly large jugular waves in nodal rhythm may be a helpful differential point.

TABLE 1.—DATA ON 12 CASES OF ATRIOVENTRICULAR NODAL RHYTHM.

Case.	Age.	Sex.	Heart disease.		Heart rate.	Nodal rhythm.		Cause of death.	Comment.
			Type.	Duration.		Cause.	Duration.		
1	42	M	Hypertensive	2 mos.	90	Hypertension	4 wks.	Uremia	
2	68	M	Hypertensive	5 yrs.	70	Hypertension	3 wks.	C.H.F.*	
3	56	M	Hypertensive	2 wks.	98	Cor. thrombosis	2 wks.	Recovered
4	62	M	Hypertensive	1 yr.	100	Cor. thrombosis	1 wk.	Cor. thrombosis	
5	52	M	Hypertensive	6 mos.	150	Hypertension	2 wks.	Recovered
6	47	M	Hypertensive	1 yr.	66	Hypertension	1 mo.	C.H.F.*	
7	65	F	Hypertensive	5 yrs.	50	Cor. thrombosis	1 wk.	Recovered
8	20	F	Rheumatic	5 mos.	66	Rheum. activity	1 mo.	Recovered
9	18	M	Rheumatic	11 yrs.	110	Rheum. activity	1 mo.	Recovered
10	84	M	Coronary	10 yrs.	150	Cor. sclerosis	1 mo.	Bronchopneumonia	
11	28	M	Syphilitic	2 mos.	76	Syphilis	3 wks.	Recovered
12	18	F	Thyrototoxic	8 mos.	150	Thyrototoxicosis	1 mo.	Postop. myoc. failure	

* Congestive heart failure.

During the past 10 years I have seen 12 instances (0.6%) of atrioventricular rhythm among 2000 patients with organic heart disease from whom electrocardiograms were available. Nine were males and 3 females, a ratio of 3 to 1. As previously reported,^{10,13b} it is an infrequent condition but one which may have important significance. It requires careful interpretation during the course of acute infectious diseases, acute coronary artery thrombosis, or when the nodal rhythm becomes chronic. Among the 12 patients who had nodal rhythm the underlying heart disease was most commonly due to essential hypertension (58.3%), but in 3 of these 7 an acute coronary artery occlusion was the precipitating cause (Table 1).

Six patients (50%) had a normal rate, 5 (41.6%) had nodal tachy-

cardia, and 1 (8.4%) had a nodal bradycardia. Although it had no relation to the cause of death, 6 patients (50%) died while the nodal rhythm was present. The duration of the nodal rhythm among those who recovered was on the average approximately 3 weeks. Digitalis was not given unless it was indicated, and among those who received this drug for the symptoms and signs of cardiac decompensation, no effect was observed on the nodal rhythm. Quinidine sulphate was not given to patients with nodal tachycardia, as this drug tends to depress the auricular musculature and to prolong the duration of the abnormal conduction. No instances of reciprocal rhythm were noted in this series. This mechanism was first described by Drury⁵ and later by Jones and White.⁹ In it the auricular contraction following the nodal impulse is sufficiently delayed so that it gives rise to a second ventricular response causing bigeminy.

The 4 illustrated cases have been appended to indicate some of the interesting features of nodal rhythm.

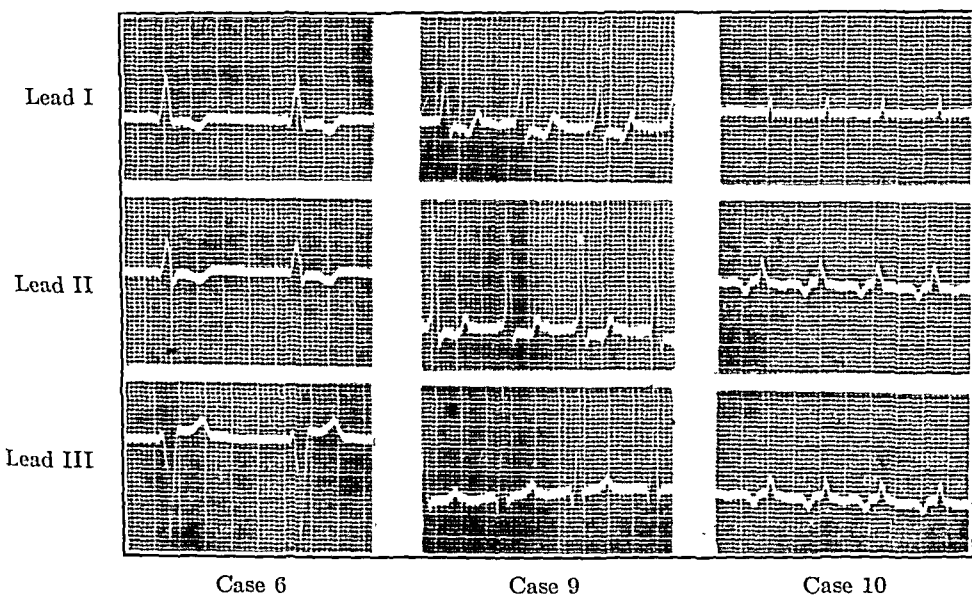


FIG. 1.—Electrocardiograms on Cases 6, 9 and 10.

Case Abstracts. CASE 6.—I. W., a 47-year-old white male, was a known hypertensive of 3 years' duration. At the age of 45 he had a cerebral hemorrhage with a resultant left hemiplegia. When first seen in December, 1937, he complained of increasing dyspnea of 3 months' duration. Physical examination revealed a blood pressure of 130/100, impaired resonance and moist râles at the bases of both lungs, a transverse cardiac diameter of 19 cm., a regular rate of 68 at the apex, the liver 4 cm. below the costal margin and tender, and moderate edema of the ankles. An electrocardiogram (Fig. 1), before digitalis was given, showed a rate of 66, marked left axis deviation, no *P* waves, and *T* waves inverted in Leads I and II. There was no response to digitalis and diuretics, and he continued to lose

ground steadily. A second electrocardiogram, repeated after 3 weeks, still showed nodal rhythm, but one taken after a month showed normal rhythm and a bundle branch block. He continued downhill and expired 6½ months after the onset of cardiac symptoms. An autopsy revealed eccentric hypertrophy of the heart, which weighed 620 gm., mural thrombi in the apex of the left ventricle, thrombosis of the left innominate, subclavian, and internal jugular veins, marked passive congestion of the liver, spleen and kidneys, bilateral hydrothorax with compression atelectasis of the basal portions of the lobes, ascites, pitting edema of the lower extremities, and passive congestion and edema of the brain.

CASE 9.—S. P., an 18-year-old white male, was known to have "heart trouble" since he was 7. He complained of dyspnea and vomiting of 2 days' duration. Examination revealed the blood pressure of 158/60 and a transverse cardiac measurement of 19 cm. There was a systolic thrill at the base of the heart, and loud rumbling systolic-diastolic murmurs over the aortic and mitral areas. Both the Corrigan and Duroziez signs were present. The liver was not palpable and no edema was noted. The cardiac rate was 110 and regular. An electrocardiogram (Fig. 1) showed a rate of 110, no visible *P* waves, and *T* in Leads I and II biphasic with a low take-off. On absolute bed rest he responded readily to digitalis and salicylates, and was well again in 3 weeks. Another electrocardiogram still showed nodal rhythm, but a third, 4 weeks after the onset, showed the presence of bifid *P* waves. The final diagnosis was rheumatic myocarditis with aortic and mitral stenosis and insufficiency with nodal rhythm.

CASE 10.—W. T., an 84-year-old white male, was known to have arteriosclerotic (coronary) heart disease for at least 10 years. He had retired 14 years before at the age of 70 and lived a life of limited activity. Two months before his death he complained of precordial and epigastric pain, dyspnea, and cough which confined him to bed. Physical examination revealed moist râles at the bases of both lungs, no apparent cardiac enlargement, a regular tachycardia of 154 beats per minute, liver 5 cm. below the costal margin and tender, marked palpable peripheral arteriosclerosis, but no edema. The electrocardiogram (Fig. 1) showed a low voltage tracing with a rate of 120, negative *P* waves, and notching of the *QRS* complexes. He responded well to digitalis and became compensated in 3 weeks. The nodal tachycardia persisted. One week later he developed a confluent bronchopneumonia which caused his death within 48 hours.

CASE 7.—D. W., a 65-year-old white female, complained of dizziness of 2 weeks' duration when first seen in August, 1933. At that time physical examination revealed a blood pressure of 160/100, heart borders within normal limits, and generalized peripheral arteriosclerosis. During the next 10 months she had an occasional complaint of headache and dizziness and the blood pressure varied between 180/120 and 140/90. In June, 1934, she suddenly became short of breath and complained of marked palpitation. When seen within a few hours the blood pressure had dropped to 100/70, and an auricular fibrillation with a rate of 150 at the apex was noted. This responded readily to quinidine, the rhythm becoming regular and the rate dropping back to 60 after 21 grains of the drug were taken orally. She felt very well until the middle of September, 1934, when a paresis of the right side of the face and the left upper extremity appeared, but this disappeared in a week. She continued well for over a year, but then began to have other attacks of auricular fibrillation, and all responded to quinidine. Attacks of the rapid irregular irregularity occurred in November, 1935; in December, 1936; in April, 1937; and in July, 1938. An electrocardiogram (Fig. 2) was taken between attacks on February 12, 1937. All 5 attacks of fibrillation occurred between midnight and 6 A.M.

On April 20, 1939, after an apparently uneventful 9 months, she collapsed

while preparing the evening meal at 5 P.M. When seen within $\frac{1}{2}$ hour she appeared to be in deep shock. No pulse was felt at the wrist and the heart tones were barely audible. She was removed to the hospital by ambulance after morphine was given for the restlessness. There, oxygen was administered by nasal catheters, and at midnight, after a lapse of $6\frac{1}{2}$ hours, the pulse became palpable at the wrist.* The rate was 50 per minute. Because of the slow rate and the severity of the attack it was thought that she had a coronary occlusion with auricular fibrillation and complete heart block. An electrocardiogram, taken the next day (Fig. 2), when her condition was poor, showed a rate of 50 per minute, no *P* waves, and regularly spaced *QRS* complexes. This tracing also suggested complete

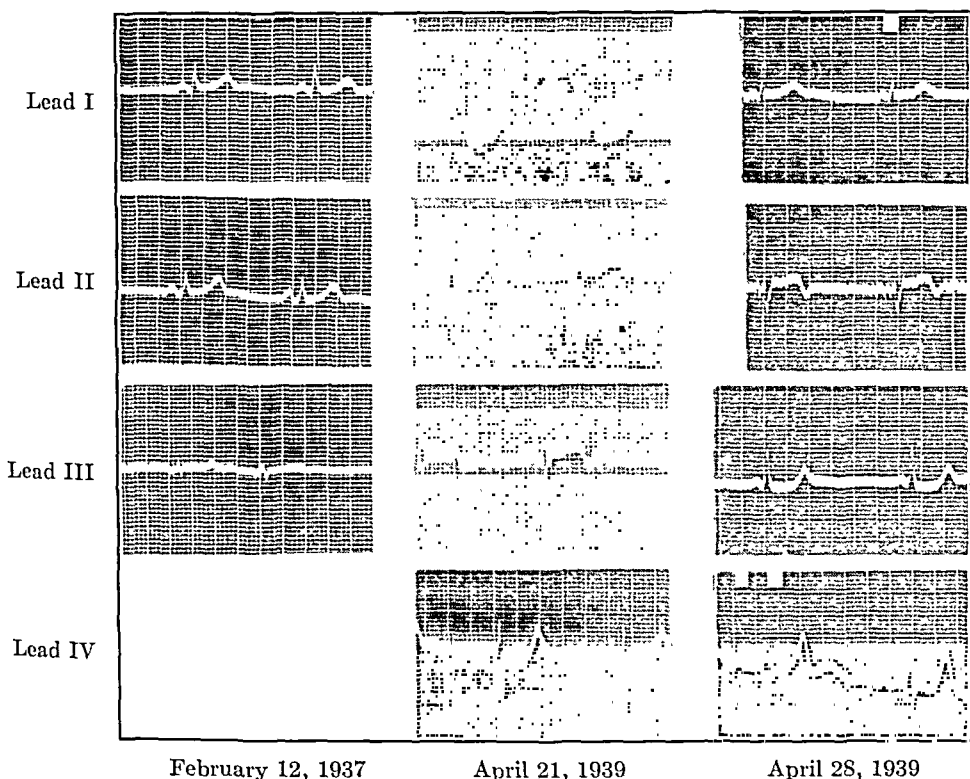


FIG. 2.—Electrocardiograms on Case 7.

heart block and auricular fibrillation, but the clinical findings indicated otherwise as she improved. The jugular pulsations were unusually large, regular, and counted at a rate of 50, and the same rate was noted over the cardiac area and at the wrist. Nodal bradycardia seemed to be more

* Robert Adams (1791–1875), a surgeon who made important contributions on cardiac subjects, noted first the sudden cessation of the pulse in a case which he considered an irregular form of angina pectoris and after an autopsy stated, "The organic seat of the gentleman's complaint was to be found in an ossified condition of the coronary arteries and aortic valves." In commenting on this (*Ann. Med. Hist.*, 1, 3d ser., 49, 1939), Dr. James B. Herrick said, "Some may question the fact that a patient with acute coronary occlusion can live for days with no perceptible peripheral pulse. I am sure, however, that this is possible. I saw one case in which no radial pulse could be felt for six or eight hours before death, the patient being quite conscious during this time. In another patient who lived for five weeks after a coronary accident there was never felt during this period more than a rapid, extremely small, thready radial pulse. For hours at a time neither nurse nor doctor could feel it at all."

likely. On April 22 her condition was much better and from then on she continued to improve during the 6-week stay in the hospital. The heart size increased from 11 cm. before the occlusion to 18 cm. after the coronary accident, and then gradually returned to the original size at the end of the 6 weeks in bed. No digitalis was given by any route at any time as there were no indications for its use. An electrocardiogram on April 25 still showed a nodal bradycardia, but one on the 28th (Fig. 2) revealed a rate of 60 and the presence of *P* waves. She returned home and remained well until October 11, 1939, when an attack of auricular fibrillation occurred again. The attacks recurred on January 19, 1940, on July 12 and September 8, and the last one to date on October 1, 1940. Since the coronary occlusion and nodal bradycardia the four attacks of fibrillation failed to respond to quinidine, but have responded to digitalis within 2 days. Also, these attacks all occurred at night. When last seen in April, 1941, she was active at home and in fair condition, complaining only of weakness.

Summary. Atrioventricular nodal rhythm is an infrequent cardiac conduction disturbance which can be diagnosed only with the aid of the electrocardiograph. Its importance rests chiefly on the two facts that it is due to a large variety of causes, both cardiac and extracardiac, and that it indicates depression of the normal pacemaker of the heart, the sino-auricular node.

Neither digitalis nor quinidine, nor any other special drug is indicated in treatment, since nodal rhythm does not tend to persist after the cause has subsided or has been removed. Treatment, if possible, should be directed against the underlying cause.

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TIBIAL ARTERY CHANGES IN COMPARISON WITH THOSE OF THE RADIAL AND CORONARY ARTERIES.

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THE observations in this study are supplementary to those reported previously in a paper on "Radial Artery Changes in Comparison with Those of the Coronary and Other Arteries."¹³ In this

paper, age period changes and arteriosclerotic changes were studied comparatively in the radial and coronary arteries from the same patient in a series of 86 cases.

In the present investigation, 61 tibial arteries were studied and compared with the radial and coronary vessels from the same case as well as with each other, to contrast the differences at various age periods. The age distribution of the 61 cases was as follows: Up to 40 years, 11; fifth decade, 13; sixth decade, 14; seventh decade, 14; eighth decade and above, 9. There were 35 males and 26 females in the group. The 61 cases covered a variety of diseases, some of which might be expected to favor vascular change: others, which are considered to have no influence in that direction. The only cases which were purposely avoided were those presenting definite signs of arterial obstruction in the extremities, as the present object was to show the average changes, individually and comparatively, in vessels of the lower extremities, as represented by the tibial artery, in cases without definite peripheral vascular disease. Thus cases of arteriosclerosis obliterans and thrombo-angiitis obliterans were excluded. The study of occluding lesions in sclerotic arteries of the lower extremities is the subject of a separate paper now under way.

In contrast to particular studies of the radial artery,^{7,8,13,15} systematic studies of the pathologic histology of the small muscular arteries of the lower extremities, as typified in the tibials, seem to be scanty. It is true that there are histologic descriptions of the arterial changes in gangrene^{2,3,16} and roentgenologic studies of calcific changes in arteries of the lower extremities,^{10,11} but investigations on age period changes and arteriosclerosis short of obstructive alterations leading to gangrene are difficult to find and seem to be confined to incidental allusions^{4,9,12} or general statements.¹

Method. In each case, sections were taken from the lower anterior tibial artery just before it passes over into the dorsalis pedis; from the radial artery at the wrist; and from the right and left circumflex and anterior descending branches of the coronary artery. These were stained with hematoxylin and eosin, and with Weigert's elastic stain and van Gieson. The studies of the tibial and radial arteries were exclusively microscopic as it is difficult to get permission for removal of these vessels at autopsy and only short sections could be taken.

Age Period and Sclerotic Changes in the Tibial Artery. In the large coronary arteries, changes with advancing age develop to a maximal degree, so marked as to make them available for meticulous analysis.^{5,6,17} Here the almost exclusively intimal changes permit the recognition, from without inward, of the musculo-elastic, elastic-hyperplastic and innermost connective tissue layers, as well as disappearance of the border between the intimal and muscular layers and the appearance of an intermediary layer there. This is capped in the late decades by eccentric, intimal, atherosclerotic develop-

ments which tend to cut down or occlude the lumen. In the smaller radial artery, these intimal details, though described by Hesse,⁸ are not as a rule discernible. Instead, there is noted the progressive splitting of the intimal elastica and the interweaving of an increasing amount of longitudinally arranged, connective tissue, forming finally and collectively a fairly uniform intimal collar gradually increasing in thickness. This thickening is relatively and actually very much less than that seen in the coronaries, and atherosclerotic changes so common in the coronaries are scarcely seen in the radials. On the other hand, medial calcification, absent in the coronaries, is frequently seen in the radial vessels.

Study of tibial artery sections in advancing decades shows, as would be expected, changes comparable with those seen in the radial artery rather than those of the coronary. A tibial artery from a stillborn showed a single layered internal elastica immediately beneath the endothelial covering. At 14 and 21 months, the tibial arteries exhibited slight splitting of this elastic layer. At 4 years, there was apparently a very slight thickening of the subendothelial layer and in an artery from a child of 5, there was slight but definite subendothelial thickening by connective tissue fibers between the split elastica. The next artery, however, from a child of 7, showed no changes, and even splitting was absent, though the corresponding coronary vessel exhibited slight atherosclerosis. At 9 years, the tibial artery presented slight subendothelial thickening. In the second decade, there was some exaggeration of these changes. But in the third decade, there was what might be termed moderate subendothelial hyperplasia with further elastic splitting. This was particularly well seen in a tibial artery from a patient of 25. And at 30, an artery showed a trace of calcification at the intimal-medial junction. An artery from a 37-year-old subject exhibited marked medial calcific sclerosis in addition to intimal changes, but this case was one of malignant hypertension and hardly a fair example of average age period changes. In the fifth decade, from 41 to 50 years, there were available for examination 13 tibial arteries, and these showed plainly an increasing degree of intimal sclerosis in the form of elastic splitting and subendothelial proliferation to form a distinct intimal collar. In contrast to the slight and moderate changes of the earlier decades, there are seen here marked intimal thickening, though this must be qualified as extreme for the tibial vessels. Not all these vessels showed marked change, 5 exhibiting moderate, and 8 marked alteration. Five of the 13 arteries (38.5%) also showed medial calcification. The sixth decade, from 51 to 60 years, furnished 14 tibial vessels for study and these showed approximately the same changes as seen in the previous decade, some arteries showing less and some more. In this period, there were 5 examples of medial calcification (35.7%). In the seventh decade, there were 14 tibials for examination, all of which showed intimal thickening,

8 of them marked. One of these vessels was occluded by an organized thrombus. Ten of the 14 vessels showed medial calcification (71.5%). Finally, there were 9 tibial arteries from subjects over 70 years, the oldest being 84. Eight of the 9 showed marked intimal thickening and 7 of the 9 medial calcification (77.8%). One vessel showed the only example of atherosclerosis in the series. Three of the 9 vessels after 70 were occluded by organized thrombi. There were thus 4 examples of tibial occlusion after 60 years of age, but all of these patients were free from definite signs or symptoms of obstruction. Of the 4 vessels showing organized occlusion, all exhibited medial calcification as well and in 1 of these the calcific change was in the form of bone formation.

Comparison of Tibial and Radial Arteries. If, now, this series of tibial arteries be compared with the radial arteries from the same patients, it will be noted that the mural changes are in a general way similar. That is to say, there first appears a splitting of the internal elastica, followed by further splitting and the development of longitudinally arranged, intervening connective tissue which increases progressively to finally and collectively form a distinct intimal collar. The amount of intimal change or sclerosis is slightly greater in the tibial artery. The difference, while not great, is usually recognizable in comparing sections of the two vessels from the same individual. It does not occur in every case and, in some instances, the radial thickening is about equal to that of the tibial or even a little greater. This feature was studied by observing the ratio of intimal thickness to medial breadth in both the radial and tibial sections. It was noted that in both the ratio of intimal to medial breadth was roughly at birth and in the first years 1 to 8. With thickening of the intima, this ratio was changed to 1 to 5 and later to 1 to 4 or 1 to 3. But when the radial ratio was 1 to 5, the tibial was not infrequently 1 to 4; and, further, when the radial ratio was 1 to 3, the tibial ratio was likely to be 1 to 2. In the seventh and eighth decades, the ratio was quite commonly 1 to 3 or 1 to 2 with the thickening slightly in favor of the tibial vessels. In comparing 57 tibial and radials, the thickening of the intima was about the same in 21, greater in the radial in 9 and greater in the tibial in 27. Of course, most of the sclerotic thickening occurs in the later years but it is especially after 60 years of age that the tibial forges ahead. Atherosclerosis was absent in the radials and was seen only once in the tibial series. As mentioned above, 4 of the tibial arteries showed organized occlusion; in the radials, there was no example of this change.

Medial calcification is a trait of the peripheral group of muscular arteries, but, as is well known, it is much more common in vessels of the lower extremities. In Lange's⁹ series of 300 cases, medial calcification was present in the radial artery in 18% and the anterior tibial artery in 83% of cases. The radial and tibial arteries exam-

ined in this study were only short single segments and it might well be that calcification was present in other portions of the vessels and not in the particular small portion here studied. Nevertheless, Mönckeberg's sclerosis was observed in 14.7% of the 61 radials and in 47.5% of the 61 tibials. Calcification was not found in the radial vessels before 50 years of age, while there were 7 examples of tibial medial calcification in the 24 vessels from cases under 50 years. After 40 years of age, the radial percentage for calcification was 18 and tibial 54; after 50 years, the radials showed calcification in 24% and the tibial in 60% of cases; after 60, the radial percentage was 26 and the tibial 74. It will thus be noted that medial calcification was roughly about three times more common in the tibial than in the radial artery. It may further be observed that this change, even in the short fragment of artery examined, was present in over one-half the cases after 50 years of age and rose progressively in incidence with each decade. The location of the calcification, while usually plainly medial, in some instances appeared first at the intimal-medial border. Even here, it seemed to be basically medial. Medial calcification, even when extensive, was not necessarily associated with extensive intimal changes. On the contrary, vessels with marked calcification often showed less intimal involvement than the average for that age. Other medial findings, such as degenerative changes suggested by a pale blue-staining reaction and rarefaction of the muscle fibers, were occasionally seen and then more commonly in the tibial than the radial artery.

These changes are illustrated in Figures 1 and 2 which show pairs of radial and tibial arteries from the same individuals at various age periods. It is difficult in microphotographs of small arteries to show satisfactorily the intimal and other details which are so readily seen in observation through the microscope. The thickening of the intima is due to like changes throughout the age periods, only increasing in amount as age progresses, and so we have attempted to show here prominently only the two chief alterations, the amount of intimal thickening and the presence of calcification. This is done by blackening in the entire intima while calcification shows for itself.

Comparison of Tibial and Coronary Arteries. Comparing the tibial arteries with the coronary vessels from the same case, it was found, as in a comparison of the radial and the coronary, that the extreme arteriosclerotic and atherosclerotic changes common in the coronaries have no parallel in the relatively slight changes in the tibial vessels. In the extreme changes due to increasing age in the tibials, the ratio of intimal thickening to medial breadth was scarcely ever more than 1 to 2, while the ratio of breadth in the coronaries between the intima and media was, in the late decades, reversed and from 5 to 1 to 10 to 1 and accompanied by advanced athero-

sclerotic changes. As in the radial, the tibial artery in its histologic alterations through age and disease gives no hint of visceral sclerosis as typified in the coronary vessels. While there were slightly greater arteriosclerotic developments and certainly much more calcification in the tibial than in the radial, this had no inferential relation to coronary sclerosis.

In the 61 cases studied there were 6 cases of clinical coronary disease all of which showed narrowing and obstruction of the coronary arteries satisfactorily supporting the clinical evidence. But in addition there were 15 symptomless cases in which there were latent coronary lesions so extreme as to produce apparently complete or almost complete closure of the vessels. There was no hint of this in the condition of the corresponding 21 tibial vessels, for while it is true that many of these vessels showed marked calcification, it is also true that there were as many or more examples of tibial calcification in which the coronary arteries showed no extraordinary changes. This, of course, is nothing new, as it has been accepted for many years that Mönckeberg's sclerosis is a peripheral type independent of visceral changes.

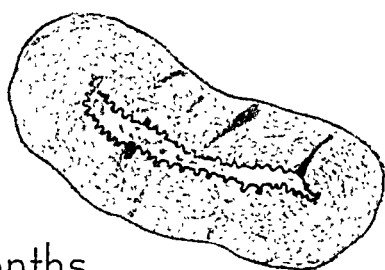
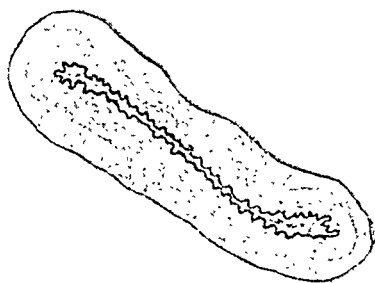
Aside from the immediate subject, which is the comparison of a type peripheral artery with a type visceral vessel, the incidence and amount of coronary sclerosis in this series of cases seems of more than passing interest. While 50 of the 61 cases were past 40 and in what might be said to be the coronary period, it yet seems remarkable that 42% of those past 40 years of age and over 50% of those past 50 showed, from the viewpoint of pathologic histology, advanced coronary disease to the degree of apparently complete or almost complete occlusion of the vessel. There can hardly be any question as to the extreme mural alteration here but whether this produces the obstruction that the microscope suggests is questioned by Stewart, Birchwood and Wells,¹⁴ who by distending with the usual pressure seemingly obstructed atherosclerotic coronary vessels found a fairly uniform lumen without evidence of constriction and conclude that "apparently the atherosclerotic plaques in coronary arteries do not necessarily protrude in the lumen during life and the apparent narrowings seen in the dead body may not have existed during life."

These sclerotic features are shown comparatively in Figure 3, which is not an exceptional but a type case. We have in our series many cases showing less radial and tibial alteration and as much or more coronary and other visceral sclerosis than illustrated here. The patient was a male negro of 47 with advanced malignant hypertension and marked encephalopathy, dying with extensive cerebral softening. There was no history of coronary attack and no clinical diagnosis of coronary disease, the symptoms being almost exclusively cerebral. Attention is called to the extraordinary thinness of the media in the cerebral vessel, made recognizable by touching

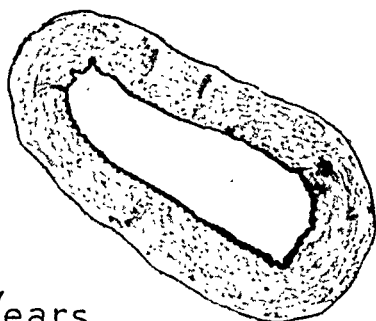
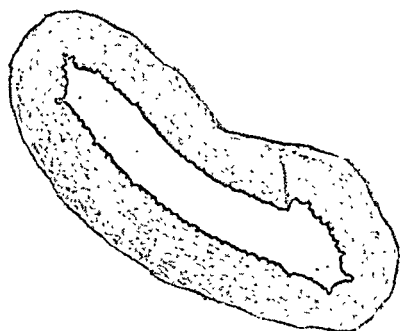
Radial

Age

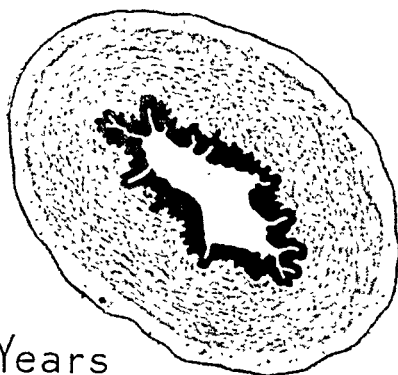
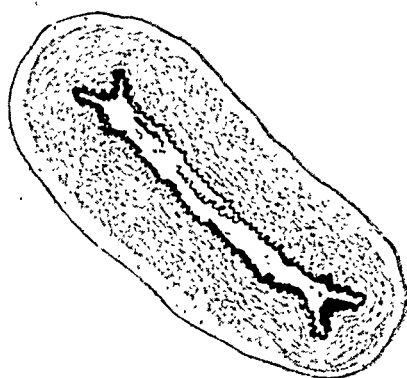
Tibial



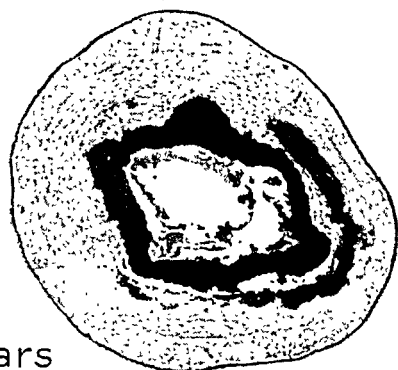
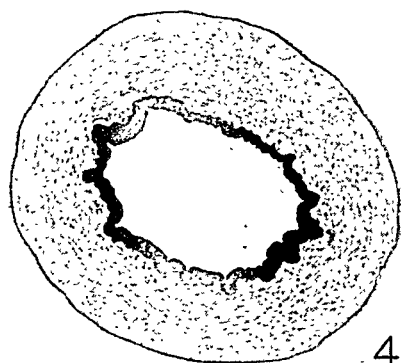
21 Months



9 Years



30 Years

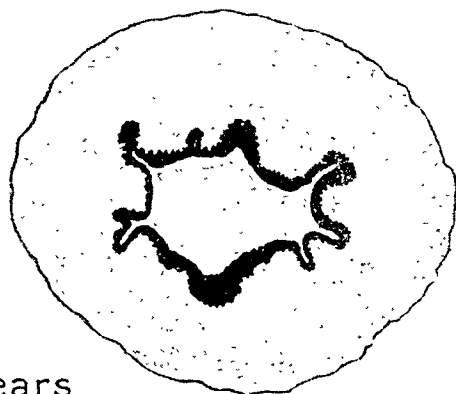
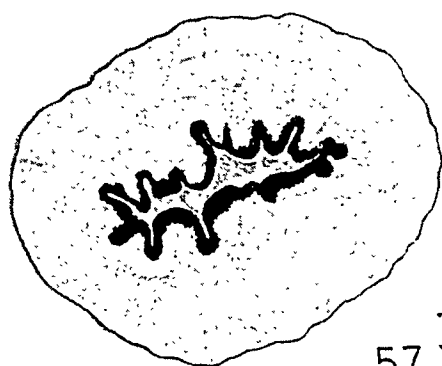


46 Years

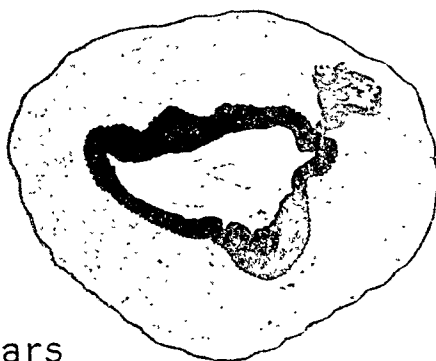
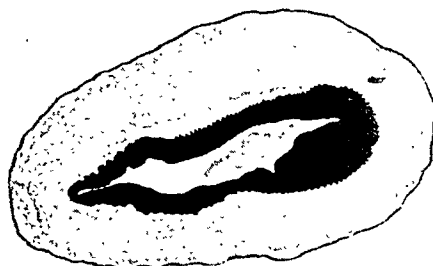
Radial

Age

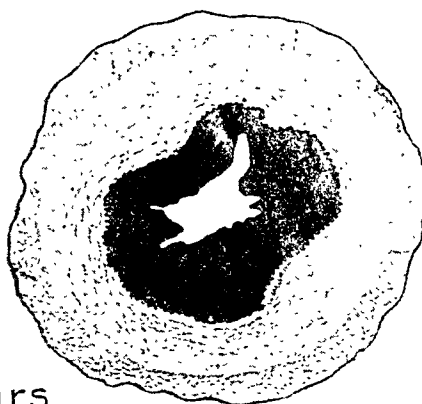
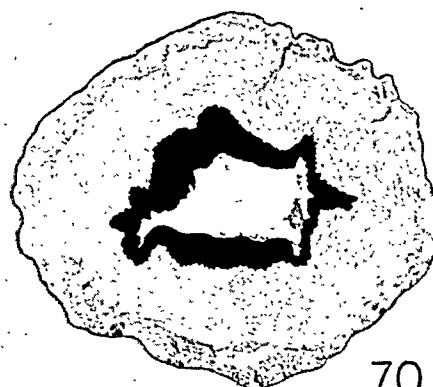
Tibial



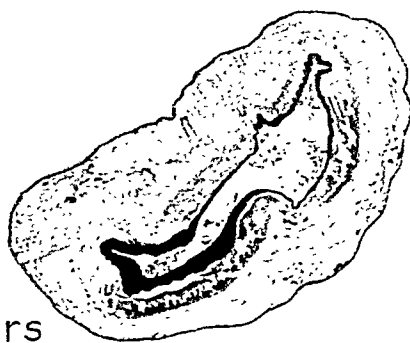
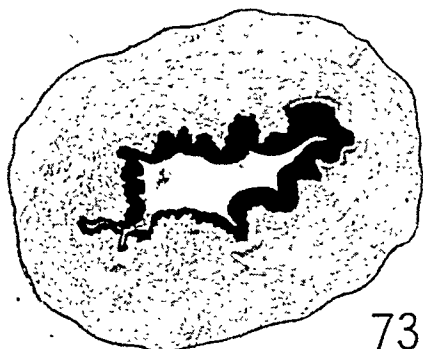
57 Years



69 Years



70 Years



73 Years

FIG. 2.

FIGS. 1 and 2.—Sections of radial and tibial arteries showing age period changes comparatively. (Hematoxylin and eosin stain, low power.) Intima blackened to show thickness directly.

(869)

up slightly the internal elastic membrane. This thinness of the media of the cerebral vessel is, as is well known, normal but it is probably partly pathologic here. The ratio of intimal to medial breadth in this vessel is 12 to 1. The intimal thickening of the radial and tibial vessels is more than usually seen in such condition and at such an age.

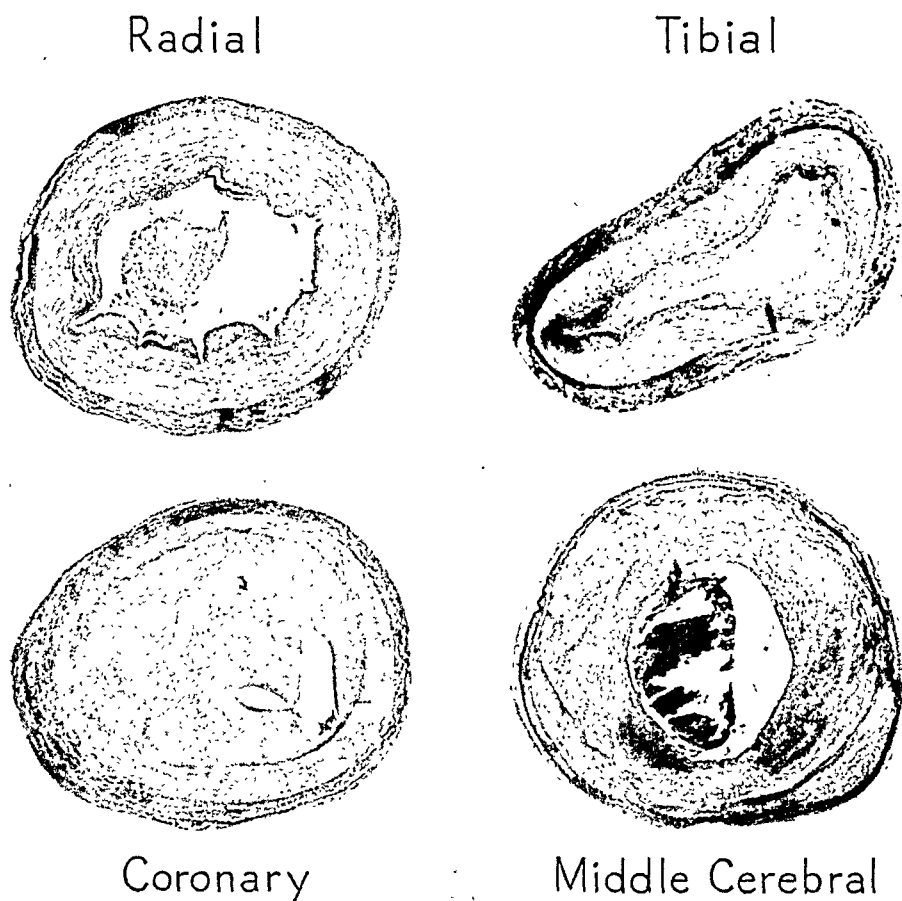


FIG. 3.—Sections of radial, tibial, coronary and middle cerebral arteries from a patient of 47 years. (Hematoxylin and eosin stain, low power.)

Examining the tibial vessels to observe specific disease effects, nothing significant was noted in this small series of cases. There were 7 cases of diabetes with no peculiar tibial, radial or coronary changes. Only 3 of the diabetic cases showed tibial artery calcification. There were 8 well-marked cases of hypertension, 7 of which showed tibial calcification, but the number is too small to have

meaning. The 4 cases showing organized occlusion of the tibial vessels were not diabetics.

Summary. Tibial artery age period changes and arteriosclerotic changes short of occlusive lesions consist of the development of a progressively thickening intimal collar of split elastica and longitudinally arranged interwoven connective tissue, together with more frequent and more voluminous medial calcification. These changes are similar to those found in the radials, but are slightly greater for the intima and decidedly greater for the media. Medial calcification was about three times more common in the tibial than in the radial in this series. Atherosclerosis is seldom a feature of tibial artery change. Altogether the intimal thickening in the tibial as well as the radial is slight, especially as compared with the coronary, and seldom threatens the integrity of the lumen. As in the radial, the anatomic condition of the tibial artery has no inferential bearing on coronary sclerosis.

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THE REACTIVITY OF INTRACRANIAL VESSELS IN THE AGED.

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A RECENT study (Cameron *et al.*)² from this Department showed that there was a strong probability that the cerebral oxygen consumption of patients suffering from psychoses of the senium was diminished. Since clearly the reactivity of the vascular system has a bearing upon the question of an adequate oxygen supply, an investigation of the integrity of this mechanism was undertaken in

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terms of the response of the systemic blood pressure to changes in position (Cameron *et al.*)¹. It was found that the slight rise in blood pressure which usually follows upon rotating the cephalic end of the body upwards and the slight fall which follows upon rotating the same end downwards through small angles was frequently reversed in persons suffering from psychoses of the senium. In these persons the blood pressure tended to be more subject to purely mechanical factors, and in consequence the pressure tended to fall in the head-up position and tended to rise in the head-down position.

This latter study was informative as to the vasomotor control as a whole. Since, however, it is well known that vascular changes with advancing age often differ considerably in different parts of the body and may be quite advanced in the intracranial vessels and barely perceptible in the vessels of the rest of the body, a means was sought which would permit of estimating the reactivity of the intracranial vessels. Many agents produce considerable change in the caliber of the cerebral vessels. Among these are CO₂, which produces cerebral vasodilatation. Amyl nitrate also produces a definite vasodilatation. Caffeine is reported as causing cerebral vasoconstriction (Merritt and Fremont-Smith⁵). Administration of these agents is, however, hard to control with the necessary precision and, with the exception of the first, these substances do not occur normally in the organism. Histamine was finally selected as a possible preparation for further investigation.

The major action of this drug is to produce dilatation of the capillaries and also of the arterioles (Carrier³). With moderate dosages a fall in blood pressure is recorded, this occurring even though constriction of the arteries is present. It is believed that this fall in pressure is due to dilatation of the capillary bed (Sollmann⁷). The pulmonary artery also shows constriction, and, since histamine produces stimulation of smooth muscle regardless of its innervation, bronchial constriction has also been reported. It is clear that, if constriction of the pulmonary artery and of the bronchi took place, even with the minute doses of histamine which we propose to use, back pressure through the right heart and superior vena cava might occur; this, in turn, could, through interference with the venous return from the brain, cause an increase in spinal fluid pressure which might be difficult to distinguish from that produced by the dilatation of the intracranial vessels. This possibility was also investigated.

Since dilatation of intracranial vessels must result in a rise in spinal fluid pressure, it was decided to attempt to study the degree of reactivity of the smaller cerebral vessels by following the rise in spinal fluid pressure produced by the intravenous injection of a standard dose of histamine. While it is generally agreed (Merritt and Fremont-Smith⁵) that the Monro-Kellie doctrine of the cranium

as a rigid container can no longer be held, yet we regard it as probable that the amount of elasticity existing in the container represented by the cranium and the spinal subarachnoid space is not so great as to preclude our being able to estimate with reasonable accuracy the relative reactivity of the vessels of the aged and the younger adult brain.

Procedure. Lumbar puncture was carried out in the lateral recumbent position. Spinal fluid pressure readings were obtained by the use of a water manometer. The pressure was recorded at minute intervals until all trends had disappeared for 10 consecutive minutes. Then 0.00025 mg. of histamine phosphate per kilo body weight was injected into an antecubital vein. Since insertion of the needle usually results in a rise in spinal fluid pressure, actual injection of the histamine was withheld until the pressure had returned to its former level. Immediately following the injection, spinal fluid pressure readings were recorded every 15 seconds for 2 minutes, at the end of which time the reaction had in the majority of cases ceased. The pulse, blood pressure and respiratory rates were recorded on the first 20 patients throughout their reaction, but, since there was no constant variation, further recording was discontinued. These studies were carried out on 38 patients suffering from psychoses of the senium and in 53 patients whose ages ranged from 20 to 50, who were suffering from early schizophrenia, alcoholism, manic-depressive states, psychoneuroses or psychopathic states.

In order to throw light on the question of whether the dosages of histamine which we employed were sufficiently large to produce bronchial spasm, constriction of the pulmonary artery and, consequently, back pressure in the venous system, we investigated the venous pressure levels concurrently with the spinal fluid pressure changes in response to the injection of a standard dose of histamine. The venous pressure readings were obtained by means of an apparatus similar to that described by Moritz and von Tabora.⁶ The venous records were taken from an antecubital vein. Simultaneous venous and spinal fluid pressure readings were taken before injection and at 5-second periods for 2 minutes after injection of the histamine. This procedure was carried out on 8 occasions in 5 patients, the group including both old and younger individuals.

Results. It can readily be seen from Table 1 that there is no tendency for histamine in the amounts used to raise the venous pressure. In the 8 investigations of this point an increased venous pressure was found on only one occasion. It was noted moreover that the rise in venous pressure persisted in this instance after spinal fluid pressure had returned to its basic level.

TABLE 1.—EFFECTS OF HISTAMINE PHOSPHATE (0.00025 MG. PER KG. BODY WEIGHT) ADMINISTERED INTRAVENOUSLY UPON SPINAL FLUID AND VENOUS PRESSURE.

Seconds.	Spinal fluid pressure.	Venous pressure.
15	+ 9	-1.75
30	+ 47	-2.25
45	+118	-6.25
60	+ 60	-5.00
75	+ 34	-3.75
90	+ 24	-4.75
105	+ 7.5	-5.00
120	+ 2.5	-4.00

Figures represent average rise or fall in terms of millimeters of water in 8 checks on 5 persons.

The data concerning the response of the spinal fluid pressure in the control group early showed that those patients who suffered from alcoholism showed a special type of response. Accordingly, the responses of the senile, alcoholic, and the remainder of the control group, which was designated the indeterminate group, are recorded separately in Table 2.

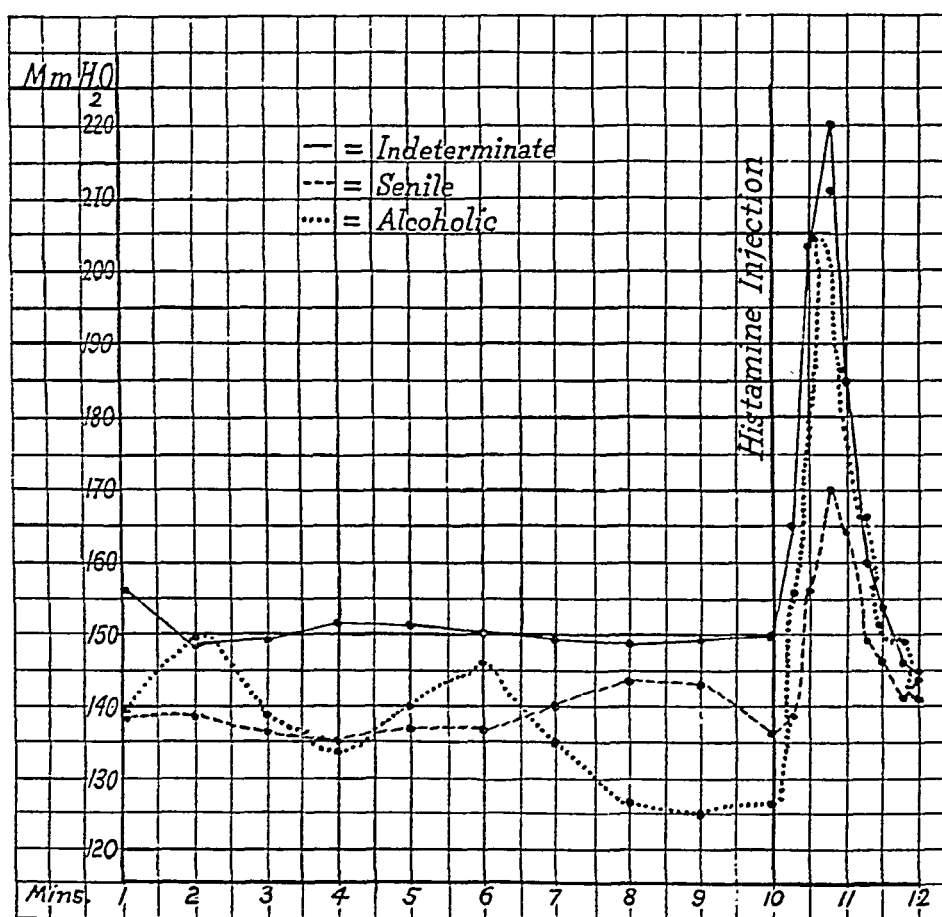


CHART 1.—Effects upon the spinal fluid pressure of histamine phosphate (0.00025 Mg. per kg. body weight) administered intravenously.

In all 3 groups the maximum rise is reached during the 45 seconds reading and in all save the alcoholics the spinal fluid pressure had returned to approximately normal levels by the 105th second. The prehistamine level was not attained in the case of the alcoholic group by the 120th second. The average rise in the indeterminate group was 70 mm. water; in the senile group it was strikingly less, being only 34 mm. water; the alcoholic group was characterized by a higher average rise, namely, 86 mm. water (Chart 1).

TABLE 2.—RANGE OF SPINAL FLUID PRESSURE RESPONSES TO HISTAMINE EXPRESSED IN TERMS OF RISE OVER BASAL LEVEL.

Pressure (mm. H ₂ O).	Per cent of cases in each category.		
	Senile.	Indeterminate.	Alcoholic.
0-20	18.91	4.34	0
21-40	29.72	8.69	7.69
41-60	8.10	39.13	7.69
61-80	13.51	8.69	23.07
81-100	10.81	13.04	23.07
101-120	8.10	13.04	15.38
121-140	5.40	8.69	7.69
141-160	0	0	7.69
161-180	0	0	0
181 up	5.40	4.34	7.69

Considerable overlap occurred, as is shown in Table 2. Two of the indeterminate group had rises of less than 34 mm. water, and 8 had rises of more than 86 mm. water; 15 of the senile group had rises of more than 70 mm. water and 8 had rises of more than 86; in the alcoholic group, 8 had rises of less than 70 mm. water, and 1 had a rise of less than 34.

Discussion. It is clear that, if we consider the senile group as a whole, there is a definite diminution of reactivity of the cerebral vessels as contrasted with that found in the younger group. The fact that considerable range of reactivity occurs within the senile group renders it possible to anticipate that by means of this method of approach an attempt may be made to differentiate groups within the senium, in which the major disability consists in a loss of reactivity of the cerebral vessels from groups in which this reactivity is relatively well preserved.

The fact that limited reactivity may be met with in younger age groups must await further study before a final explanation can be given. Clearly, one must consider the possibility that it may be ascribable to the abnormal psychiatric condition from which the individual was suffering; it may, on the other hand, be quite independent of this and represent the amount of variation usually found within a series of subjects. If the latter is the case, one may suggest that, while relatively little reactivity of the cerebral vessels may permit of adequate cerebral functioning during younger adult years, this limitation may become of more serious moment later on when a slower circulation time, a diminished cardiac output and a lowered blood oxygen-carrying power begin to result in chronic cerebral anoxemia.

The increased reactivity of the alcoholic group is rather difficult to explain. It is noted, however, that considerably more difficulty was experienced in obtaining a steady base line in the alcoholic group. This was due to the amount of emotional tension. It seems possible that this tension may also be accountable for the increased rise in the spinal fluid pressure in response to histamine. In this connection it should not be forgotten that it has been reported that

there is pathological evidence to suggest that excessive alcoholic indulgence tends to reduce the probability of arteriosclerosis (Leary⁴).

Summary. 1. A method is reported for investigating the reactivity of the cerebral vessels by observation of the spinal fluid pressure changes after intravenous injections of histamine.

2. A series of 38 senile and 55 psychiatric patients at younger age levels was examined.

3. The average rise in spinal fluid pressure in the senile group was 34 mm. of water; the average for 29 alcoholics included in the younger group was 86 mm. of water; and the rise for the 26 remaining patients in the younger group was 70 mm. of water.

4. The bearing which this may have on possible cerebral anoxemia in the aged was considered.

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THE EFFECT OF PREGNANCY UPON EXPERIMENTAL HYPERTENSION IN THE RABBIT.*

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WOMEN afflicted with chronic arterial hypertension usually suffer some aggravation of their disease if they become pregnant. No satisfactory explanation has yet been offered for this unfavorable influence of pregnancy. One obvious means of studying this phenomenon is afforded by observing the blood pressure during pregnancy in animals previously made hypertensive by the experimental induction of renal ischemia, for it is believed that the latter plays a rôle in at least several of the forms of chronic hypertension observed in child-bearing women (Goldblatt²).

Harrison, Grollman and Williams,⁵ found that gestation tends to lower the level of a pre-pregnancy hypertension in rats.† This result is the reverse, therefore, of what might have been anticipated from clinical experience. That such a finding is probably to be

* Aided by a grant from the Commonwealth Fund.

† Since this article was submitted for publication, two others have appeared which must be mentioned here. Page, *et al.*⁶ report that pregnancy brings about a lowering of blood pressure in both the rat and rabbit, and Dill, *et al.*¹ failed to find any alteration in blood pressure during repeated pregnancies in rabbits.

expected among laboratory animals is suggested by the observations of others. Thus, Pickering and Prinzmetal⁷ did not note any unfavorable effect of pregnancy upon chronically hypertensive rabbits, and Goldblatt³ found that during pregnancy, most hypertensive dogs exhibited a slight or moderate fall of pressure. It is noteworthy, however, that no information is available concerning the effects of pregnancy upon the arterial tension of normal animals. For this reason we have investigated the influence of pregnancy upon both normal and renal ischemic rabbits.

Materials and Methods. Observations were made upon does of miscellaneous racial stocks for periods ranging from 3 to 6 months. Only healthy, mature animals, of proven fertility, and weighing more than 2.5 kg. were studied. They were housed in individual cages, and were fed a standard complete ration in the form of pressed dry pellets.* Body weight was taken at weekly intervals.

Blood pressure determinations were made once weekly, except during pregnancy, when they were made twice a week or daily. The ear-capsule method of Grant and Rothschild⁴ was used. For this purpose the animals were trained to lie quietly upon an electrically warmed pad without the use of a restraining harness. A period of 2 to 3 weeks was utilized in accustoming each animal to this technique. Pressures were recorded only when determinations, made at consecutive 30-second intervals, were constant to within 4 mm. of Hg.

Blood samples were taken once weekly by arterial puncture and analyzed for blood urea nitrogen by the method of Van Slyke and Cullen.⁹ Blood uric acid determinations also were run on these samples, but since no significant variations were noted, these results have not been included in the data which follow. Specimens of urine were collected at weekly intervals and analyzed for protein by a quantitative technique.⁵

Varying degrees of renal ischemia were produced in 16 animals by the method of Pickering and Prinzmetal.⁷ A clamp was applied to the left renal artery, and after an interval of 3 to 10 days, the right kidney was removed. Effort was made to obtain 2 types of result: *a*, persistent arterial hypertension, and, *b*, a borderline grade of ischemia insufficient to produce an elevation of blood pressure, or at most, sufficient to cause only a transient hypertension. The latter group was studied in the expectation that pregnancy might unmask a hypertension which was presumably latent under these conditions; in the event of failure to do so, these animals could be utilized as blind operation controls. In the animals operated upon, a period of 10 to 12 weeks was allowed to elapse, and any elevations of pressure were permitted to become stabilized, before the animals were mated.

In addition to observations made upon normal non-pregnant animals for the purpose of establishing control data, the studies concerning the effects of pregnancy include data derived from 21 animals, as follows: *a*, 5 intact normal rabbits; *b*, 11 rabbits in which the attempt to produce renal ischemia had resulted in no elevation, or only transient elevation, of blood pressure, and in which the arterial tension was therefore essentially normal at the time of mating; and, *c*, 5 rabbits in which the operative procedures had resulted in a conspicuous elevation of blood pressure, maintained at hypertensive levels for at least 3 weeks prior to mating.

Observations. Prior to Pregnancy. Data concerning the levels and fluctuations of blood pressure and blood urea, and the incidence of proteinuria among non-pregnant does, are summarized in Table 1.

* Supplied as Rockland Rabbit Ration and containing 17% protein.

TABLE 1.—RENAL ISCHEMIA IN RABBITS.

(Systolic blood pressure, blood urea nitrogen and proteinuria in non-pregnant does, observed for periods of 1 to 3 months.)

Animals.	Blood pressure.		Blood urea nitrogen.		Proteinuria.	
	Determinations.	Mean, mm. Hg.	Determinations.	Mean, mg. per 100 cc.	Urine exams.	Positive.
Normal (17)	176	80.0 \pm 4.8	46	16.4 \pm 2.9	10	3
Ischemic, non-hypertensive (11)	91*	85.7 \pm 9.2	14*	24.4 \pm 4.7	13	5
Ischemic, hypertensive (5)	50*	128.6 \pm 12.0	14*	23.4 \pm 3.7	18	11

* Determinations made after the B.P. had become stabilized in its permanent postoperative range.

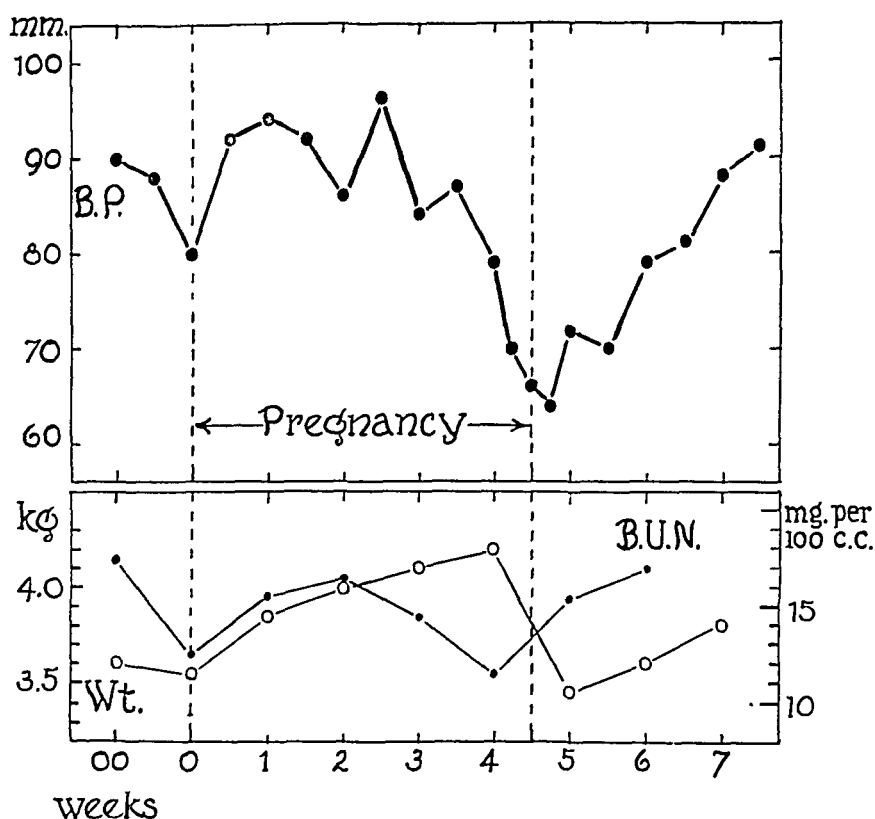


CHART 1.—Normal Rabbit 709. Effect of pregnancy upon systolic blood pressure (B.P.), body weight (Wt.) and blood urea nitrogen (B.U.N.). This rabbit delivered 8 living pups at term. Note the sharp fall in blood pressure just before delivery and the gradual return to normal during the postpartum period. The B.U.N. variations noted here are characteristic of the control group and are not great enough to be considered significant.

every particular that of the group described in the preceding paragraph.

Pregnancy. The changes in a typical normal rabbit are illustrated in Chart 1. Chart 2 demonstrates the constancy of these changes among normal rabbits, and the data of Table 2 indicate their extent. Thus, it was found that pregnancy caused no appreciable alteration in the systolic blood pressure until the last 7 days of gestation. During that time, a significant and constant fall was noted. This drop, which was usually equivalent to over 20% of the pre-pregnancy tension, reached its maximum at or shortly following labor. This low pressure returned to the pre-pregnancy level quite gradually, during the first 2 to 3 weeks post partum. These changes of pressure were accompanied by no evidences of ill health, since the coincidental changes in body weight, as well as the duration of pregnancy and size of litters, were normal. The blood urea levels during pregnancy showed no significant fluctuations.

TABLE 2.—RENAL ISCHEMIA IN RABBITS.

(Influence of pregnancy upon body weight, systolic blood pressure and blood urea nitrogen.)

Animals.	Mean body weight, kg.	Mean blood pressure, mm. Hg.	Mean blood urea N, mg. per 100 cc.	Protein- uria.
<i>Normal (5):</i>				
Beginning of pregnancy	3.6	82	16	1
Term	4.0	64	15	0
2 wks. postpartum	3.7	83	14	3
<i>Ischemic, non-hypertensive (11):</i>				
Beginning of pregnancy	4.4	88	25	3
Term	4.5	71	19	9
2 wks. postpartum	4.3	81	23	8
<i>Ischemic, hypertensive (6):</i>				
Beginning of pregnancy	4.2	126	22	2
Term	4.4	97	19	4
2 wks. postpartum	4.3	126	21	3

Entirely analogous changes were observed among the 11 animals operated upon whose blood pressures were normal at the time of mating. The only characteristic exhibited by this group, and not seen in normal rabbits, was a tendency of the blood urea to fall at the end of pregnancy. This was not infrequently accompanied by proteinuria.

The same changes were also exhibited by the 5 hypertensive rabbits. A typical protocol is illustrated in Chart 3. Both Chart 3 and the data in Table 2 indicate that the hypertension which was present at the beginning of pregnancy in this and in the remaining animals, was not accompanied by elevations of blood urea which could be considered uremic in character. Not only did pregnancy fail to aggravate the chronic hypertension of these animals, but, as in the control groups, it depressed the level of both the

pre-pregnancy blood pressure and blood urea nitrogen. The depressions, moreover, were of the same order as they were among the control animals.

In only one instance were the results otherwise than as described. In Rabbit 5, whose protocol is illustrated in Chart 4, the pre-labor fall of blood pressure was cut short at the 28th day of gestation. Thereafter, it rose rapidly and continued to do so throughout the

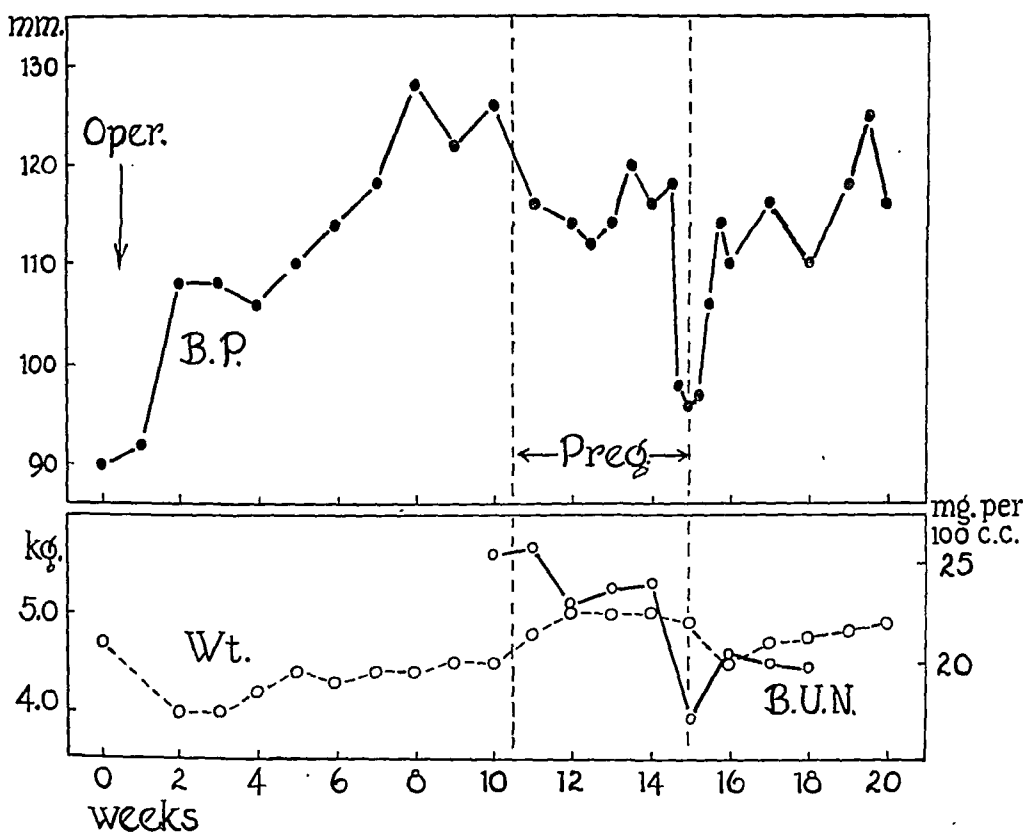


CHART 3.—*Renal hypertension in Rabbit 428.* Effect of pregnancy upon systolic blood pressure, body weight and blood urea nitrogen. This animal delivered 8 living pups at term. Note that the degree of pressure fall is similar to that in the normal animal (Chart 1) and that the fall is sharp near the time of delivery with a more gradual return to normal during the postpartum period. The decrease in level of B.U.N. at or near term was constant in this group.

remainder of pregnancy and the ensuing post-partal period. The later stages of this rise were accompanied by uremia, from which the animal ultimately succumbed on the 10th post-partal day. It is noteworthy that the pups of this animal were macerated and sub-normal in weight, indicating that intra-uterine death had probably occurred at about the time in pregnancy when the unusual sequence of events was initiated.

Miscellaneous Observations. Table 3 indicates that the average duration of pregnancy and the size of the litters in all groups were normal.

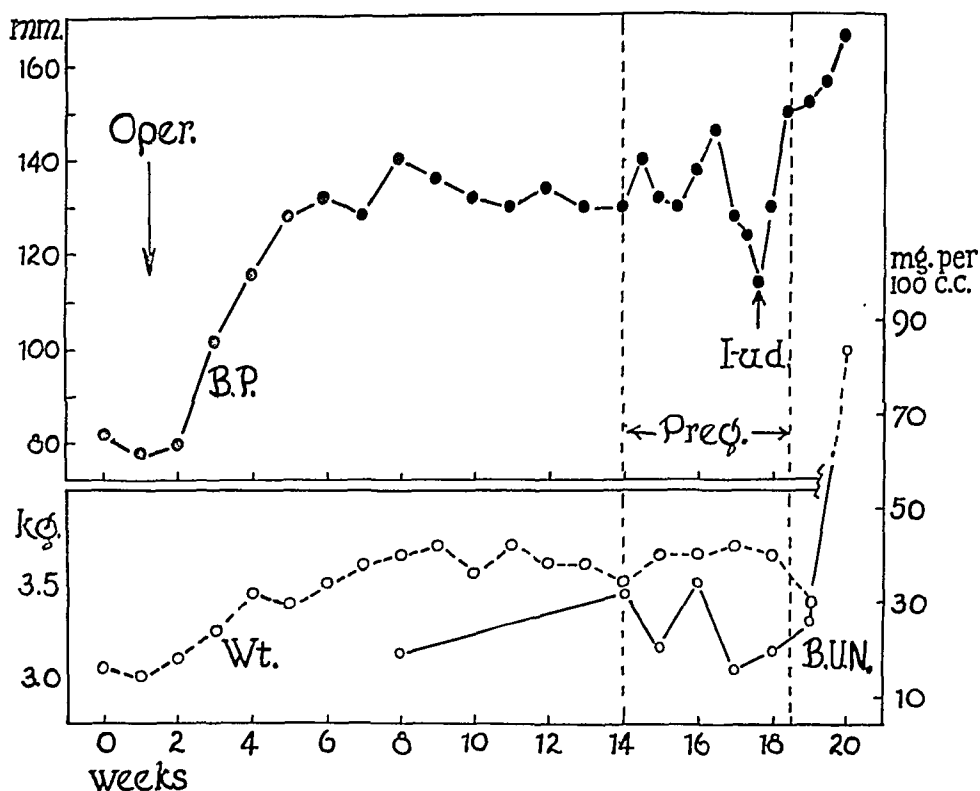


CHART 4.—Renal hypertension in Rabbit 5. Effect of pregnancy upon systolic blood pressure, body weight and blood urea nitrogen. Intra-uterine death (I-ud) of fetuses? We believe that there is a reasonable evidence that the pups in this case died about the time the blood pressure ceased to fall and suggest that the presence of viable pups temporarily delayed the ultimate course of events.

Analysis of our data indicates that the extent of the pre-labor fall in blood pressure among the various groups of animals was closely related to the number of fetuses present *in utero*. This relationship is illustrated in Chart 5.

TABLE 3.—RENAL ISCHEMIA IN RABBITS.
(Data concerning pregnancy.)

Animals,	Average duration of gestation, days.	Average size of litters, pups.
Normal (5)	32.2	6.4
Ischemic, non-hypertensive (11)	31.7	5.4
Ischemic, hypertensive (6)	32.8	5.7

Discussion. Our results confirm the previous observations that pregnancy does not aggravate the arterial hypertension which can be produced in experimental animals by the induction of renal

ischemia. This failure to produce an experimental result incorporating the features of a syndrome observed in clinical medicine is probably due to one of two facts: Either the nature of this experimental hypertension differs from that seen in the child-bearing woman, or the physiology of pregnancy in the rabbit, dog and rat differs in those particulars which account for the pressure changes observed in the human.

Our data, moreover, show that the fall in arterial tension which pregnancy causes in hypertensive animals can also be demonstrated in non-hypertensive animals. Since this observation has not been

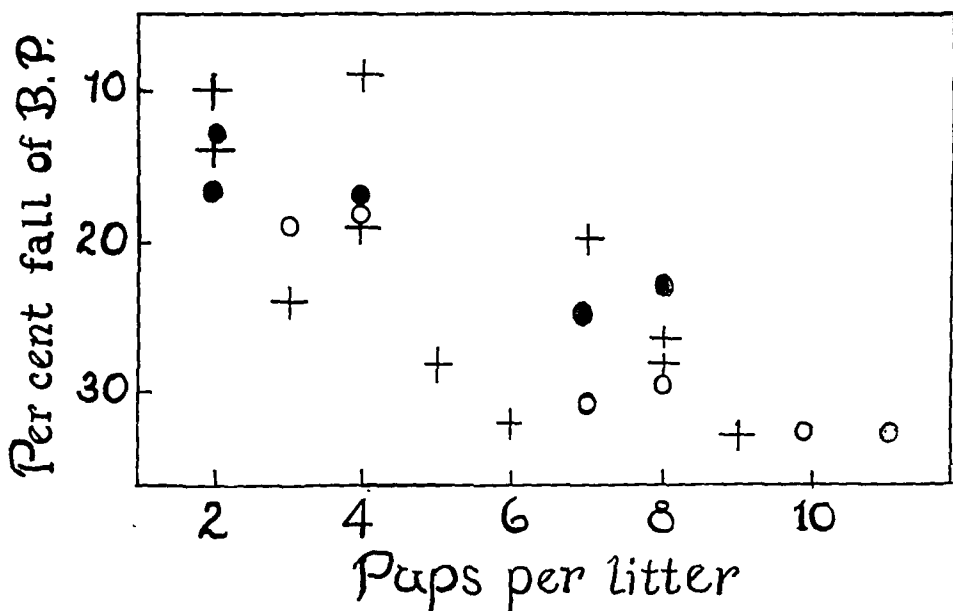


CHART 5.—Per cent fall of maternal blood pressure in relation to size of litter. O = normal rabbits. + = ischemic, non-hypertensive rabbits. ● = hypertensive rabbits. Calculated as the per cent difference between the level during the pre-pregnancy control period and the last pressure recorded before the onset of labor. Note that the fall of pressure is greater as the number of pups per litter increases and that it is of the same general order regardless of surgical procedures or pre-pregnancy level.

made previously, it is necessary that caution be exercised in ascribing to pregnancy any specific beneficial effect upon experimental hypertension. The production during pregnancy of a specific antipressor substance cannot be postulated in the light of these results, unless there is evidence that the pressor substance which it presumably neutralizes is a factor in the maintenance of normal arterial tension.

The nature of the mechanism which brings about the pre-partal fall of pressure is obscure. While it is apparently concerned with the number of fetuses *in utero* at the time the fall occurs, any assumption that a humoral factor elaborated by the products of conception

is responsible, or that local hemodynamic factors are the cause, must be examined in the light of the fact that the depression is maintained for a prolonged period following delivery.

Summary. A study was made of the fluctuations in: *a*, blood pressure; *b*, blood urea; and, *c*, in the excretion of urinary protein during pregnancy in normal rabbits, and in rabbits in which arterial tension was previously raised by the experimental induction of renal ischemia.

It was found in both groups of animals that pregnancy tended to bring about a lowering of the systolic pressure a few days before the onset of labor. The extent of this fall amounted to about 20% of the pre-pregnancy tension. The return of pressure to the pre-pregnancy level occurred gradually during the first 2 to 3 weeks post partum.

In the normal animal these fluctuations of arterial tension were not accompanied by significant alterations of blood urea, nor by proteinuria. In the renal ischemic animals, however, there was a coincidental, slight, pre-partal fall of blood urea, and a tendency to proteinuria. In no animal was there evidence to indicate that these changes were due to ill health. The normal gestational increase of maternal body weight took place, the pregnancies were normal in duration, and the number of pups born was normal for this species.

The extent of the pre-partal fall of blood pressure was proportionate to the number of fetuses present.

It is a pleasure to acknowledge the capable assistance of Miss Isabella Fullerton and of Miss E. H. Shiels, of the Department of Pharmacology, who performed the chemical determinations.

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FIBRILLARY TWITCHINGS.

AN INVESTIGATION OF THEIR SITE OF ORIGIN.

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For many years it has been commonly believed that fibrillary twitchings are caused by irritation or degeneration of the cells of the anterior horn of the spinal cord. This hypothesis, like many

other hypotheses in medicine, has been stated so repeatedly that it has become accepted as a fact, even though it has no better basis than the frequent association of fibrillary twitchings with neurologic diseases in which there is evidence of a lesion of the spinal cord. Fibrillary tremors are helpful in the recognition of such diseases, but they also occur in other conditions, some of them harmless and not, so far as is known, resident in the central nervous system. The exact mechanism of production of fibrillary twitchings in muscles has never been accurately described.

One of the most informative contributions was that of Denny-Brown and Pennybacker.¹ According to these authors, beginning on the fifth day after denervation of a muscle, a fine fibrillation may be seen. This is associated with a particular sensitivity to acetylcholine. These authors also found, in cases of amyotrophic lateral sclerosis, bulbar palsy and progressive muscular atrophy, that a fibrillary twitch was accompanied by a single large action current. This was determined by means of a needle electrode and appropriate recording devices. The group of fibers involved in the "fasciculation" is smaller than a muscle fasciculus, but much larger than a single muscle fiber. The only functional group of this nature in muscle is the motor unit. Denny-Brown and Pennybacker inferred from their observations and the pathology of the disease that the disorder underlying fasciculation was situated in the nerve fiber or in the parent cell of the anterior horn, probably the latter.

Our desire was to determine whether or not the current idea of the central origin of fibrillation in such diseases as progressive muscular atrophy, progressive bulbar paralysis and amyotrophic lateral sclerosis was correct, or whether there was some peripheral mechanism at work which accounted for the fibrillation. Investigation of this point alone seemed simple, as one had only, by some mechanical means, to interrupt the nervous pathway between the cells of the anterior horn and the involved muscle. It seemed logical that if, by means of some anesthetic agent, the intervening nerve pathway was interrupted and fibrillation continued, one could assume that there was some peripheral mechanism wholly or in part responsible for the development of the fibrillation.

Protocol. An elderly man who registered at this clinic in February, 1940, suffering from amyotrophic lateral sclerosis with generalized fibrillary twitchings in both lower extremities, was desirous of having us carry out any type of investigation which might throw some light on the etiologic factors responsible for his condition. To effect spinal anesthesia, 70 mg. of procaine in 2 cc. of cerebrospinal fluid was administered. Complete motor and sensory paralysis was obtained well above the level of the umbilicus. Biopsy of the left gastrocnemius muscle was carried out while anesthesia persisted. It was clearly seen that the fibrillary twitchings in the exposed and other muscles continued unchanged. A few days later, peripheral

block of the left common peroneal nerve was done, using metycaine (benzoyl- γ -[2-methylpiperidino]-propanol hydrochloride). In spite of the complete foot drop and complete peroneal anesthesia, there was no visible change in the diffuse fibrillary twitchings of the involved peroneal muscles.

The observations of Denny-Brown and Pennybacker would seem to require, in the explanation of "fasciculation" at least, some activity on the part of the motor neuron. Our observations of a patient with amyotrophic lateral sclerosis, and also of another patient with the same disease, would seem to exclude the bodies of the cells of the anterior horn as the site of involvement, as fibrillation in the lower extremities persisted under the influence of spinal anesthesia or block of the nerve to an involved area. Indeed, the observations suggest some alteration in the response of the neuromuscular unit at its periphery, presumably to a chemical agent. Although these observations do not explain the phenomenon of fibrillation, they indicate that future studies of fibrillation should be addressed to the peripheral portions of the neuromuscular unit rather than to the cell body itself.

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ANIMAL EXPERIMENTS CONCERNING THE HORMONAL THERAPY OF TESTICULAR ATROPHY.*

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IN PREVIOUS communications we endeavored to show that both in the male and in the female, the gonad-stimulating actions of androgens and estrogens are direct, peripheral effects while the gonad-inhibitory actions of these same compounds are indirect and merely the result of an inhibition of gonadotropic hormone production by the hypophysis^{3a,b}. The view was also expressed that the reason why the same steroid may either inhibit or stimulate the gonad depending on the dosage used, is simply that the optimal dosage range for the direct (stimulating) and the indirect (inhibitory) effect is not the same. In the same experimental series, we

* The expenses of this investigation were defrayed by a grant in aid received from the Schering Corporation of Bloomfield, N. J.

also noted that the gonadal atrophy produced by a number of agents, which presumably suppress gonadotropic hormone production by the pituitary, can be inhibited by treatment with such doses of steroid sex hormones as are required for the direct stimulation of the gonad. It seemed of interest to extend these experiments to such instances of gonadal atrophy which are known to result from direct damage to gonadal tissue and not merely to suppression of gonad-stimulating pituitary activity. In the present communication, we report experimental evidence in which the action of androgens was studied after testicular damage produced by cryptorchidism or Roentgen ray treatment of the gonad itself.

Experiment 1: Five groups of 6 young male albino rats of an average body weight of 58 gm. were treated as follows: Two groups were irradiated, two were rendered bilaterally cryptorchid, and the final group served as untreated controls. Three weeks later, daily subcutaneous treatment with 10 mg. testosterone in 0.4 cc. of peanut oil was initiated in one group of irradiated and one group of cryptorchid animals and continued for 21 days. On the day after the last injection, all animals were sacrificed and the organs taken for weight and histological study. The method of irradiation was as follows: Under nembutal (pentobarbital sodium) anesthesia, the animals were laid on their backs, shielded with lead, only the scrotum and lower limbs being exposed. Radiation to a total of 800 r was given (at 110 KV, 0.7 ma, through 1 mm. Al) within 15 minutes. This dosage was chosen as being that most likely to produce complete but not irreparable atrophy.¹ Table 1 summarizes the data.

TABLE 1.—EFFECT OF DELAYED TESTOSTERONE TREATMENT ON TESTES DAMAGED BY ROENTGEN RAYS OR CRYPTORCHIDISM.

Treatment.	Testes wt.*	Single testis wt.		Sem. ves.	Prost.	Histology.
		In scrotum.	In abdomen.			
Untreated	2.214	1.107	...	0.266	0.421	Normal histologic structure
Irradiated	0.606	0.303	...	0.245	0.334	Inhibition of spermatogenesis; Leydig cells large
Irradiated plus testosterone	0.444	0.223	...	1.034	0.721	Inhibition of spermatogenesis; Leydig cells atrophic
Cryptorchid	1.250	0.878 (3)	0.372 (5)	0.247	0.320	Inhibition of spermatogenesis; Leydig cells large
Cryptorchid plus testosterone	1.008	0.762 (3)	0.246 (3)	1.285	0.823	Inhibition of spermatogenesis; Leydig cells atrophic

* Since in some cases descent of one testis occurred in the cryptorchid groups, the weights of these intraabdominal testes are compared with the weights for single testes in other groups. The number of testes on which the average weight is based is given in parentheses.

The Roentgen ray conditioned atrophy was fairly complete as shown by the testis weight of 0.606 gm. as compared with 2.214 gm. in the normal. Testosterone was ineffective in restoring the testis

to or towards normal, indeed the testes of the treated animals were even more atrophic, weighing only 0.444 gm. Histologically, complete inhibition of spermatogenesis accounted for the marked loss of weight. The more pronounced atrophy in the treated groups was probably due to the concomitant interstitial cell atrophy caused by testosterone. In the cryptorchid groups, the abdominal testis averaged 0.372 gm. for uninjected animals and 0.246 gm. for the injected. Here again the greater atrophy in the case of injected animals was presumably due to interstitial cell atrophy. Our material confirms the almost generally accepted rule that destruction of spermatogenic cells, by agents such as Roentgen rays or cryptorchidism, goes hand in hand with an increased development of interstitial cells. The atrophy of the Leydig cells caused by testosterone is probably due to the fact that this steroid inhibits the gonadotropic hormone secretion of the hypophysis. We also noted that the seminal vesicles and prostates did not respond as well to testosterone in the irradiated animals as in the cryptorchid (1.034 gm. compared with 1.285 gm. for seminal vesicles, and 0.721 gm. compared with 0.823 gm. for prostates). This should be emphasized in view of the fact that the action of testosterone on these accessory sex organs is evidently direct. Thus the observations support the conception that Roentgen ray treatment may inhibit the direct actions of androgens. This series of experiments appeared to indicate that the direct stimulating effect of testosterone on the testis is ineffective after direct damage to the gonad. The following experiment was performed to test the possibility that this irresponsiveness of the testis might not develop if no time was allowed between intervention and treatment to permit gonadal atrophy to occur.

Experiment 2: Groups comparable to those of the first experiment having an average body weight of 58 gm. were treated during 21 days in the same way as above, except that injections of testosterone in the appropriate groups began on the day following the interventions. On the 23d day of the experiment, the animals were sacrificed and the organs taken for weight and histologic study. Table 2 summarizes the data.

TABLE 2.—EFFECT OF IMMEDIATE TESTOSTERONE TREATMENT ON TESTES DAMAGED BY ROENTGEN RAYS OR CRYPTORCHIDISM.

Treatment.	Testes wt. (gm.).	Sem. ves.	Prostate (mg.).
Untreated	1.382	56 mg.	132
Irradiated	0.547	34 mg.	116
Irradiated plus testosterone . .	0.484	574 mg.	419
Cryptorchid	0.556	39 mg.	102
Cryptorchid plus testosterone .	0.615	1.019 gm.	634

Again both irradiation and cryptorchidism significantly reduced the testis weight, while injection apparently was ineffective in offsetting this atrophy. The fact that testosterone stimulated the

accessory sex glands far less effectively in the irradiated than in the cryptorchid group (0.574 gm. compared to 1.019 gm. for seminal vesicles, and 0.419 gm. compared to 0.634 gm. for the prostate) is even more striking than in the previous series.

It appears from these observations that if the testis is directly damaged, by transposition into the abdomen or exposure to Roentgen rays, it cannot be stimulated by testosterone whether treatment is initiated immediately following, or some time after the testicular damage. This insensitivity to the direct stimulating action of testosterone is in striking contrast with the obvious beneficial effects obtained by androgens in the previously quoted experiments in which testicular atrophy was induced by agents which presumably suppress the gonadotropic hormone production of the pituitary.

To complete our study of the hormonal therapy of testicular atrophy further experiments were performed on hypophysectomized animals. The literature on the action of steroid hormones on the testes of hypophysectomized animals has been discussed in previous publications^{2,5} and is therefore omitted here. Suffice it to say that testosterone is capable of inhibiting the testis atrophy caused by ablation of the hypophysis. This stimulating action is therefore obviously not mediated by the pituitary gland. The interstitial cells, on the other hand, are not stimulated by testosterone after hypophysectomy, and actually undergo atrophy under the influence of this hormone in the intact animal. It appeared of interest to establish whether the interstitial cell inhibiting action of the hormone is likewise direct or whether it is merely due to inhibition of gonadotropic hormone secretion by the hypophysis. In order to establish this point, further experiments had to be performed in hypophysectomized males in which the interstitial cells were maintained in a well-developed condition by daily treatment with gonadotropic preparations. If the inhibitory action of testosterone were direct, it should be evident in the Leydig cells of animals thus treated,

LEGENDS FOR FIGS. 1 TO 6.

FIG. 1.—Testis of hypophysectomized untreated rat showing inhibition of spermatogenesis and atrophy of the interstitial cells.

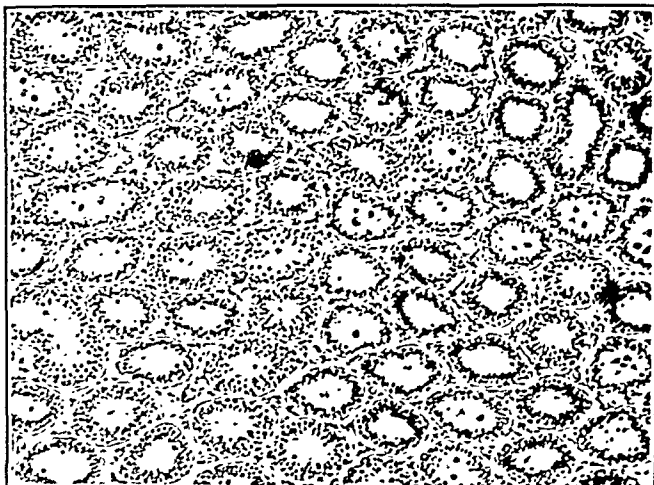
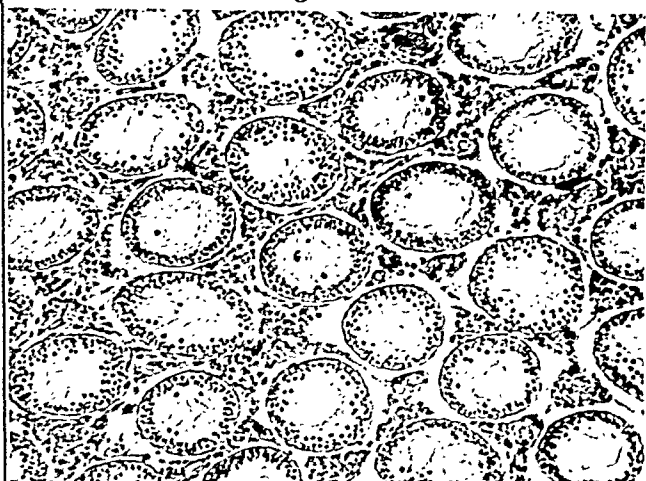
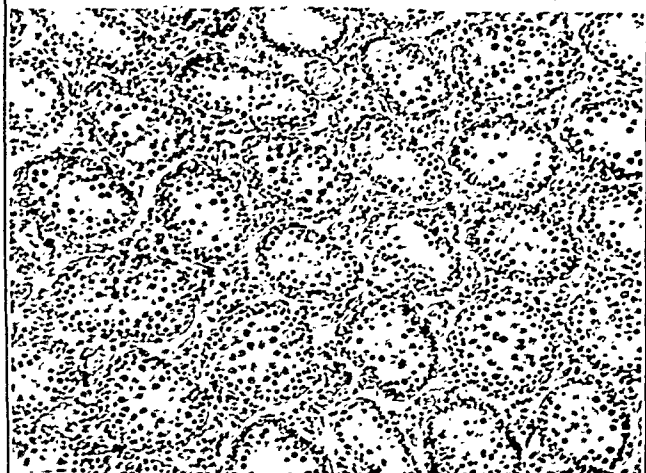
FIG. 2.—Testis of hypophysectomized rat treated with L.H. Note inhibition of spermatogenesis and the numerous large interstitial cells.

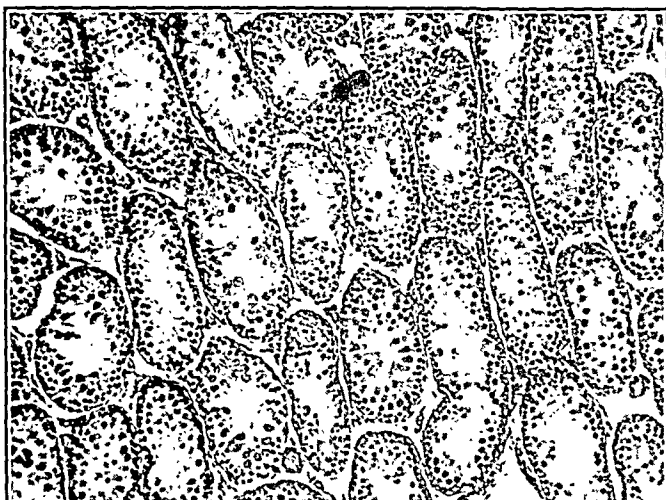
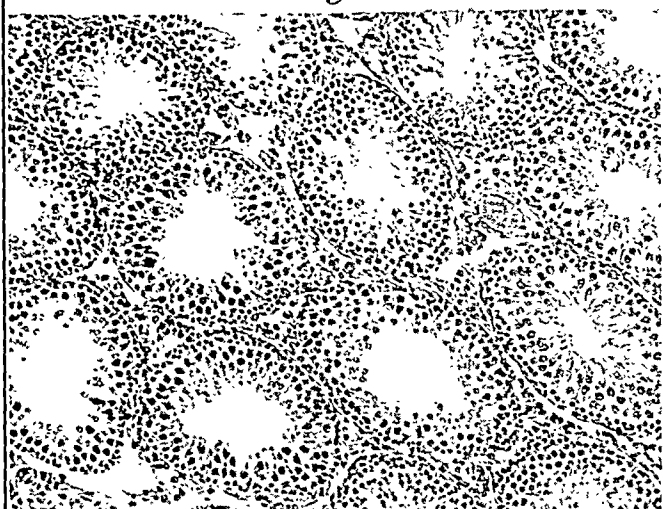
FIG. 3.—Testis of hypophysectomized rat treated with L.H. and testosterone. Note partial restoration of spermatogenic activity. The interstitial cells are large and numerous as in Figure 2.

FIG. 4.—Testis of hypophysectomized rat treated with testosterone. Note partial restoration of spermatogenesis and atrophy of interstitial cells.

FIG. 5.—Testis of hypophysectomized rat treated with F.S.H. Note almost full range of spermatogenesis. Simultaneous development of interstitial cells may be due to traces of L.H. in the extract used.

FIG. 6.—Testis of hypophysectomized rat treated with F.S.H. and testosterone, showing almost full restoration of spermatogenic activity and moderately developed interstitial cells.

*Fig. 1**Fig. 2**Fig. 3*

*Fig. 4**Fig. 5**Fig. 6*

but if it were due to a decrease of the normal gonadotropic hormone secretion of the pituitary, no effect could be expected in hypophysectomized rats receiving gonadotropic hormone by injection. In this connection, it is of interest that in female hypophysectomized rats estrogens do not cause the development of the large corpora lutea usually formed under the influence of such compounds in the intact animal. On the other hand, if the estrogens are given to hypophysectomized rats in combination with gonadotropic extracts, large corpora lutea are readily formed. This proved a peripheral synergism between gonadotropic hormones and estrogens in the female.⁴ In view of these findings, it appeared important to establish whether a similar coöperation exists between the androgens and the gonadotropic hormones in the male. The following experiment was performed to clarify these points.

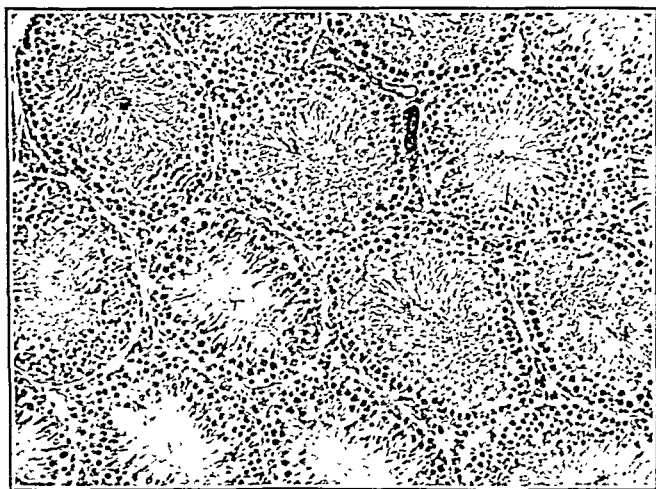


FIG. 7.—Testis of normal control rat.

Experiment 3: Seven groups of 6 male albino rats each with an average body weight of 86 gm. were treated as follows: Group 1, intact controls treated with oil; Group 2, hypophysectomized controls, treated with oil; Group 3, hypophysectomized treated with a luteinizing hormone (L. H.*); Group 4, hypophysectomized treated with L.H. and testosterone; Group 5, hypophysectomized treated with testosterone; Group 6, hypophysectomized treated with a follicle stimulating hormone (F.S.H.*); Group 7, hypophysectomized treated with F.S.H. and testosterone. The former was administered in doses of 100, the latter in doses of 50 I.U. in aqueous solution subcutaneously once daily. Testosterone was given sub-

* "A.P.L.," a purified pregnancy urine preparation made by Ayerst, McKenna and Harrison, Ltd., Montreal, was used as a source of L.H., and "Antex," a pregnant mare serum preparation made by Løvens Kemiske Fabrik, Copenhagen, was employed as a source of F.S.H.

cutaneously once daily in doses of 10 mg. in 0.4 cc. of peanut oil. A period of 14 days was allowed to elapse between the hypophysectomy and the initiation of treatment in order to permit severe testis involution, the animals were then treated for 14 days and sacrificed on the 29th day after hypophysectomy. In the course of the experiment, 3 animals in Group 4 and 2 in Group 7 succumbed. The gross weight of the testes of these animals which has been mentioned in another connection for comparative purposes^{3c} is given in Table 3 together with the most outstanding histologic changes observed. Characteristic sections of the gonads of each group are illustrated in Figures 1 to 7.

TABLE 3.—EFFECT OF SIMULTANEOUS TREATMENT WITH TESTOSTERONE AND GONADOTROPIC HORMONES ON TESTES AFTER HYPOPHYSECTOMY.

Treatment.	Testes wt. (gm.).	Histology.
Normal controls	2.257	Normal
Hypophysectomy controls	0.164	Marked atrophy of germinal epithelium and Leydig cells
Hypophysectomy plus L.H.	0.532	Marked atrophy of germinal epithelium, stimulation of Leydig cells
Hypophysectomy plus L.H. and testosterone	0.607	Moderate atrophy of germinal epithelium, stimulation of Leydig cells
Hypophysectomy plus testosterone	0.394	Slight restoration of spermatogenesis, atrophic Leydig cells
Hypophysectomy plus F.S.H.	1.040	Normal spermatogenesis, large Leydig cells
Hypophysectomy plus F.S.H. and testosterone	0.960	Normal spermatogenesis, large Leydig cells

From these data, it appears that L.H. stimulates only the interstitial cells. This action may explain the slight increase in gross weight. F.S.H. stimulates the germinal epithelium as shown by the restoration of spermatogenic activity and consequently there is a significant increase in weight. The fact that this F.S.H. preparation also caused slight stimulation of the Leydig cells should probably be ascribed to traces of L.H. which may have been present in the commercial extract used. Testosterone stimulates the germinal epithelium and thus also causes partial restoration of weight but fails to influence the interstitial cell. Testosterone in combination with L.H. did not prevent the Leydig cell development caused by the latter, but synergized L.H., inasmuch as it induced considerable development of spermatogenic cells which was not seen in rats receiving L.H. alone. In the group injected with F.S.H. and testosterone, the Leydig cells were also well developed.

From these observations, we may conclude that the inhibitory action of testosterone on the Leydig cells is indirect and due to a decrease in the rate of gonadotropic hormone secretion.

Summary. In the rat, large doses of testosterone—which suffice to inhibit the testis atrophy produced by hypophysectomy, or agents which depress the gonadotropic hormone secretion of the pituitary—cannot counteract the testis involution due to direct

damage to the gonad by interventions such as Roentgen ray treatment or cryptorchidism. It appears that the latter agents render the testis insensitive to the stimulating action of androgens. The seminal vesicles and prostate likewise become relatively insensitive to testosterone following direct Roentgen ray treatment.

In hypophysectomized rats, gonadotropic pregnancy urine extracts stimulate only the interstitial cells but have little or no effect on the spermatogenic epithelium. When given in combination with large doses of testosterone, the luteinizing hormone of pregnancy urine retains its interstitial cell stimulating action. This indicates that the interstitial cell atrophy produced by similar doses of testosterone in intact animals is not due to a direct effect on these cells themselves, but probably to an inhibition of the gonadotropic hormone production by the pituitary. In the case of simultaneous administration of luteinizing hormone and testosterone, a synergism is noticeable, inasmuch as the interstitial cell development caused by the former is added to the germinal epithelium stimulating action of the latter. In experiments in which a pregnant mare serum preparation was administered to hypophysectomized rats both the spermatogenic epithelium and the interstitial cells showed signs of stimulation and neither of these effects was significantly modified by large doses of testosterone. There appears to be no marked synergism between the germinal epithelium stimulating action of pregnant mare serum preparations and testosterone.

The authors are especially indebted to Drs. Gregory Stragnell and Erwin Schwenk of the Schering Corporation for the testosterone, and to Dr. Stanley Cook of Ayerst, McKenna and Harrison, Ltd., of Montreal for the A.P.L. used in these experiments.

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BOOK REVIEWS AND NOTICES

PHYSIOLOGY OF THE FETUS. Origin and Extent of Function in Prenatal Life. By WILLIAM FREDERICK WINDLE, Professor of Microscopic Anatomy, Northwestern University Medical School. Pp. 249; 70 illustrations, and 27 tables. Philadelphia: W. B. Saunders Company, 1940. Price, \$4.50.

THE increasing interest in fetal and neonatal morbidity and mortality in obstetric and pediatric circles makes this monograph particularly timely. The book should be especially useful to those in research fields, and it provides the means for supplementing courses in embryology with the functional aspects of development. Those interested in behavior problems of children may find here knowledge of prenatal physiology which is often germane to their investigation. The book is divided into 15 chapters, each of which discusses the physiology of a particular system. The author devotes four chapters to the nervous system, with a final chapter to fetal nutrition and metabolism.

The introduction takes up comparative fetal physiology with reference to the selection of experimental material to be used in different problems. The author stresses that in the physiology of the fetus one is dealing with two organisms maintaining mutual although often precarious relationships to one another. In the discussion of the fetal heart he refers to the various clinical phenomena of interest to obstetricians, and sets out the theories which have been propounded to explain them. There is an excellent chapter on fetal circulation, including consideration of the mechanism which brings about the functional closure of the ductus arteriosus at birth.

In the discussion of the mechanism of fetal respiration the author leans to Henderson's theory of asphyxia at birth. The question as to whether or not the fetus normally aspirates amniotic fluid is answered.

The four excellent chapters on the physiology of the nervous system consider the genesis of function, fetal nervous activity and the eventual development of fetal motor reaction, reflexes, and fetal sense. Of particular interest today is the consideration of the fetal endocrine glands, in which the author states, *inter alia*, "we cannot be sure that fetal insulin plays any part in protecting the diabetic mother." A discussion of the various types of placenta, and comparative physiology of the nutrition and metabolism terminates the text. An appropriate bibliography is found appended to each chapter.

This critical interpretation and appraisal of many scattered observations on the physiology of the fetus should be of particular interest and value in research and clinical fields in which the problems of reproduction and fetal life are encountered.

P. W.

TUMORES PRIMITIVOS MALIGNOS BRONCO-PULMONARES. Cancer, Sarcoma, Linfogranuloma. By JULIO PALACIO, Adjunct Professor of Clinical Medicine in the Medical Faculty of Buenos Aires; Director of the Municipal Dispensary for Respiratory Tract, and EGIDIO S. MAZZEI, Adjunct Professor of Medicine in the Medical Faculty of La Plata; Chief of Clinic in Professor Castex's Department; Chief of the Section on Human Pathology of the Research Institute. (Vol. III, Biblioteca Argentina de Medicina Interna.) Pp. 401; 129 illustrations and 4 colored plates. Buenos Aires: "El Ateneo," 1940.

THIS study of primary malignant tumors of the lung constitutes the third volume of a Biblioteca Argentina de Medicina Interna. It is based

on 120 cases observed in Professor Castex's clinic, the majority of which was confirmed at necropsy. Most of the work concerns "broncho-pulmonary cancer" (carcinoma) with shorter sections on sarcoma (various types) and lymphogranuloma (Hodgkin's disease). The various aspects of the subject are considered—incidence, etiology, pathology, diagnosis, prognosis, treatment—with especial emphasis on the radiologic study and on more than 20 clinically distinguishable sub-varieties. The book is well printed, well illustrated and contains a copious bibliography of 58 pages. It is a valuable contribution to a subject that is being actively investigated at the present time.

E. K.

PATHOLOGICAL CONFERENCES HELD AT THE COOK COUNTY HOSPITAL BY DR. R. H. JAFFÉ. Edited by CHESTER C. GUY, M.D. Pp. 1164; 1 illustration. Chicago: Cook County Hospital Internes' Alumni Association, 1940. Price, \$3.50. (For sale by Chicago Medical Book Company, (Chicago, Illinois.)

For nearly ten years the late Dr. Jaffé held weekly clinical-pathologic conferences at the Cook County Hospital in Chicago. These conferences were largely attended by staff and visitors, and probably were of particular value to the interns and residents. As a tribute and memorial to Dr. Jaffé, the Cook County Hospital Internes Alumni Association has collected notes on 596 conferences and made them available to a larger public. Each case report averages approximately two printed pages. The clinical notes are summarized by the attending physician, after which Dr. Jaffé tells of the lesions observed at the autopsy, pointing out features of interest, and discussing the pathogenesis of the lesions. The subjects selected cover a wide field. A good index adds much to the value of the book. This carefully prepared collection of case studies should prove of especial interest to those practitioners who are unable frequently to attend well-conducted post-mortem examinations.

B. L.

THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE HEART. By HENRY A. CHRISTIAN, M.D., Sc.D. (Hon.), LL.D., F.A.C.P., Hon. F.R.C.P. (Can.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University; Physician-in-Chief, Emeritus, Peter Bent Brigham Hospital, Boston, Mass. (Reprinted from Oxford Monographs on Diagnosis and Treatment.) Pp. 599; 28 figures. New York: Oxford University Press, 1940.

WRITTEN for the enlightenment of graduate physicians, this book presents the author's mature knowledge concerning the clinical diagnosis and the treatment of heart disease. According to the introduction: "This book is based in the main on the personal experience of the author obtained in the study of patients and their records at the Peter Bent Brigham Hospital, Boston, Mass., and in office and consultation practice . . ." "So far as is possible, the correct diagnosis, anatomical, etiological and functional, is to be sought, and treatment is to be based on this diagnosis, in order that the best results are to be attained."

W. J.

DISEASES AFFECTING THE VULVA. By ELIZABETH HUNT, B.A., M.D., CH.B. (Liverp.), Honorary Physician to the Skin Department, South London Hospital for Women; Honorary Dermatologist, New Sussex Hospital for Women and Children, Brighton, etc. Pp. 215; 36 illustrations and 18 plates in color. St. Louis: The C. V. Mosby Company, 1940. Price, \$4.50.

THIS monograph, written from the standpoint of a dermatologist, is an excellent exposition of the subject and is beautifully illustrated. The 18 color plates lend to a more complete understanding of the subject. Some

of the plates show lesions of the oral mucous membranes side by side with similar lesions of the vulva and vagina. The author has described not only the usual skin disease but discusses thoroughly the neoplastic lesions found in this area, and has a series of excellent chapters on the vulvar manifestations of venereal diseases. The last chapter of the book is devoted entirely to vulvar conditions found in young children. The author concludes that kraurosis represents a late stage of leukoplakia and is thus opposed to the view that the two are distinct diseases.

The thorough consideration of all factors, especially hormonal influences, concerned with the diseases of this area and the very full sections on histopathology and treatment should make the book of especial value to the dermatologists and gynecologists.

P. W.

THE EXTRA-OCULAR MUSCLES. A Clinical Study of Normal and Abnormal Ocular Motility. By LUTHER C. PETER, A.M., M.D., Sc.D., LL.D., Professor Emeritus of Diseases of the Eye in the Graduate School of Medicine of the University of Pennsylvania; Consulting Ophthalmologist in the Rush Hospital for Consumption and Allied Diseases, The Friends' Hospital for Nervous and Mental Diseases and the Roxborough Memorial Hospital. Pp. 368; 147 illustrations and 5 colored plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$4.50.

THIS third edition of the author's well-known book on the extraocular muscles needs no introduction to those who specialize in ophthalmology. The author's clear concise style should appeal to all graduate students in this specialty. The chapter on nystagmus was written in collaboration with Dr. J. C. Yaskin and exemplifies his characteristic concise didactic teaching.

This book is to be recommended as a text for all those who propose to take up the study of ophthalmology.

F. A.

DISEASES OF THE DIGESTIVE SYSTEM. Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine, Rush Medical College of the University of Chicago; Attending Physician, Michael Reese Hospital; Consulting Physician, Cook County Hospital, Chicago. (Fifty Contributors.) Pp. 952; 176 illustrations. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.

THIS book constitutes the first comprehensive presentation, in a single volume, of the entire field of gastro-enterology, including the diseases of the liver and the pancreas. Not only are the anatomy, the physiology and the organic and functional disturbances of the digestive tract fully covered, but also the gastro-intestinal aspects of those diseases that primarily affect other systems of the body. In addition the endocrinologic, the allergic, and, to a limited extent, the vitamin deficiency factors which enter into the production of digestive tract disease are clearly outlined.

In the preparation of the book Dr. Portis, as editor, has secured the assistance of 50 collaborating physicians. Each of them has been chosen because of his ability to make an authoritative presentation in his special field of interest. This, of course, has led to some repetition and inconsistencies, but on the whole the work may be regarded as an able presentation of the current opinions on the subject of gastro-enterology. In most instances when argumentative points are discussed ample references to the original literature are made.

The arrangement of the text is satisfactory, and the illustrations, with the possible exception of those on the intestinal parasites, are excellent.

Dr. Portis is to be congratulated on the production of a book for which there has been a long felt need, not only by the medical student but also by the general practitioner.

V. M.

MEDIZIN UND KULTUR. Gesammelte Aufsätze von Paul Diepgen. Edited by W. ARTLETT, E. HEISCHKEL, and J. SCHUSTER. Pp. 309. Price, Paper, Rm. 21; Bound, Rm. 22.80. **DAS PHYSIKALISCHE DENKEN IN DER GESCHICHTE DER MEDIZIN.** By PROF. DR. MED. ET PHIL. DR. H. C. PAUL DIEPGEN. Pp. 39. Price, Rm. 2. Stuttgart: Ferdinand Enke, 1938 and 1939.

THESE medico-historic essays are from the pen of the Director of the Berlin Institute of the History of Medicine. "Medizin und Kultur" contains more than a score of Diepgen's articles, prepared between 1910 and 1936. It was produced for his 60th birthday on November 24, 1938. The selections illustrate his special interest in the practical significance of medical history; in historiography, folk medicine, medieval medical history, the history of gynecology, and so on.

Most of these essays were composed in calmer times, times more auspicious for historic study. The seven (or eight?) that were first published since the advent of Hitlerism, naturally have more than an average interest for Anglo-Saxon readers. One wonders, for instance, whether the occurrence in the same article of two such statements as: "It is no accident that the ever strengthening democratic and liberal thought among Europeans occurred in the period of modern biology and the theory of evolution" and "it is the totalitarian consideration of medicine that German National Socialism demands of him" (*i. e.*, the good physician), indicates a conflict in the writer's mind between conviction and expediency, or whether the point of view of German thought has so changed that such statements now assume a logical sequence for the author. In the earlier essays, the author frequently evinces his appreciation of the truly democratic in medical and civic progress. Let us hope that he may live to see truly democratic principles reestablished in his Fatherland! In the meantime, what can be expected from a German university professor, when he is told by the Minister of Justice, as Raymond Fosdick quotes, that he "must ask himself one question: does my scientific work serve the welfare of National Socialism?"

E. K.

STUDIES ON TUBERCULOSIS. The Spread of Tuberculosis in Negro Families of Jamaica, B.W.I. By E. JOYCE SAWARD, PERSIS PUTNAM, and EUGENE L. OPIE. The Fate of Negro Persons of a Tropical Country, Jamaica, B.W.I., after Contact with Tuberculosis. By EUGENE L. OPIE, PERSIS PUTNAM, and E. JOYCE SAWARD. A Survey of Tuberculous Infection in a Rural Area of East Alabama. By A. W. GRAHAM, P. W. AUSTON, and PERSIS PUTNAM. The Fate of Persons Exposed to Tuberculosis in White and Negro Families in a Rural Area of East Alabama. By A. H. GRAHAM, P. W. AUSTON, and PERSIS PUTNAM. Pp. 198; illustrated. Baltimore: The Johns Hopkins Press, 1941. Price, \$1.10.

THIS monograph is composed of four articles reprinted from a recent number of the *American Journal of Hygiene*. It deals with two continuing investigations, supported by the Rockefeller Foundation, on the epidemiology of tuberculosis, with special reference to the spread of this disease in the Negro race. The studies reported, as is well known, represent outstanding work in this field, in which experts in pathology, clinical diagnosis, epidemiology and statistical treatment of data have combined in the analysis of data collected over a period of many years under conditions well suited to provide significant information. In general, the results call attention to the vital importance of environment in the spread of Negro tuberculosis and furnish strong support to the view that tuberculosis of the reinfection type in adolescents and adults is exogenous rather than endogenous. Within the monograph the results previously secured by the authors and their colleagues are incorporated, so that the volume, in its compact form, is a convenient source book for the study as a whole.

E. L.

PHYSICAL CHEMISTRY FOR STUDENTS OF BIOLOGY AND MEDICINE. By DAVID INGERSOLL HITCHCOCK, PH.D., Associate Professor of Physiology in the Yale University School of Medicine. Pp. 264; 22 illustrations. Third Edition (with laboratory experiments). Springfield, Ill.: Charles C Thomas, 1940. Price, \$3.50.

WE welcome a new edition of this well written and interesting textbook on the laws of dilute solutions. These solutions constitute for the medical student the most important part of physical chemistry. Useful features are the problems to be worked out by the student, and directions for a series of 20 laboratory experiments. For the physician who wishes to brush up on physical chemistry, the chapters on hydrogen ions, colloids, equilibria in blood, and enzyme action are especially useful, and knowledge of higher mathematics is not required. For the present edition much of the material has been rewritten.

M. McC.

NEW BOOKS.

A History of Medicine. By ARTURO CASTIGLIONI, M.D., Formerly Professor at the University of Padua; Research Associate in the History of Medicine at Yale University. Translated from the Italian and Edited by E. B. KRUMBHAR, M.D., PH.D., Honorary President of the American Association of the History of Medicine. Pp. 1053; 443 illustrations. New York: Alfred A. Knopf, 1941. Price, \$8.50.

The Pharmacological Basis of Therapeutics. A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students. By LOUIS GOODMAN, M.A., M.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine, and ALFRED GILMAN, PH.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine. Pp. 1383; 126 illustrations. New York: The Macmillan Company, 1941. Price, \$12.50.

Physical Medicine. The Employment of Physical Agents for Diagnosis and Therapy. By FRANK H. KRUSEN, M.D., F.A.C.P., Associate Professor of Physical Medicine, The Mayo Foundation, University of Minnesota; Head of the Section on Physical Therapy, The Mayo Clinic, etc. Pp. 846; 351 illustrations. Philadelphia: W. B. Saunders Company, 1941. Price, \$10.00.

The Conducting Properties of the Human Organism to Alternating Current. By THOMAS ROSENDALE. Pp. 195; 68 figures and 42 tables. Copenhagen: Einar Munksgaard, 1940. Price, Dán. Kr., 15.

Techniques of Conception Control. By ROBERT LATOU DICKINSON, M.D., Former President, American Gynecological Society, and WOODBRIDGE EDWARDS MORRIS, M.D., General Medical Director, Birth Control Federation of America. Pp. 56; 50 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, 50c.

Examination Questions in Laboratory Methods. Pp. 134: Bacteriology, 34; Clinical Pathology, 24; Blood Chemistry, 7; Hematology, 40; Tissue, 3; Basal Metabolism, 1; Parasitology, 6; Serology, 8; Miscellaneous Medical Subjects, 11. Compiled and published by The Gradwohl School of Laboratory Technique, St. Louis, Mo., 1941.

Milk Sickness Caused by White Snakeroot. By EDWIN LINCOLN MOSELEY, Professor Emeritus of Biology, State University, Bowling Green, Ohio; Past-President of Ohio Academy of Science. Pp. 171 (lithoprinted); 3 illustrations. Bowling Green, Ohio: The Ohio Academy of Science and The Author. Price, \$1.00.

A monograph by a layman on an intoxication produced in cattle by eating a weed, white snakeroot, and in man usually by drinking the milk of poisoned animals. The disease, which has a high fatality rate in cattle and in man, and occurs in rural communities, especially in the Ohio Valley, was long a subject of controversy. The historical aspects of the monograph are therefore of particular interest.—R. K.

Cardiac Classics. A Collection of Classic Works on the Heart and Circulation with Comprehensive Biographic Accounts of the Authors. Fifty-two Contributions by Fifty-one Authors. By FREDRICK A. WILLIUS, M.D., M.S. in Medicine, Chief, Section of Cardiology, The Mayo Clinic; Professor of Medicine, The Mayo Foundation for Medical Education and Research, The Graduate School, The University of Minnesota, and THOMAS E. KEYS, A.B., M.A., Reference Librarian, The Mayo Clinic; Formerly Carnegie Fellow, The Graduate Library School, The University of Chicago. Pp. 858; illustrated. St. Louis: The C. V. Mosby Company, 1941. Price, \$10.00.

"*True Comics*," Vol. 1, No. 1, a Bimonthly Magazine. DAVID T. MARKE, Editor. Pp. 17; illustrated. New York: The Parents' Institute, Inc., 1941. Price, 60c a year.

"Pediatricians and parents are increasingly concerned about the overstimulating effect of the increasingly lurid 'comic' magazines. . . . As an antidote, the publishers of Parents' Magazine are launching a new magazine for boys and girls of all ages called 'True Comics,' similar only in format to the present 'comic' magazines. It differs radically in subject matter and editorial treatment." A number of pediatricians, psychologists and educators have already signified their approval of this interesting new venture in child psychology.—E. K.

The Heart in Pregnancy and the Childbearing Age. By BURTON E. HAMILTON, M.D., Cardiologist, since 1921, to The Boston Lying-In Hospital, Boston, and K. JEFFERSON THOMSON, M.D., Associate Physician, Metropolitan Life Insurance Company Sanatorium, Mt. McGregor, N. Y.; Research Associate in Medicine, Albany Medical College, etc. With a Section entitled "Delivery and Obstetrical After-Care of Cardiacs" by FREDERICK C. IRVING, M.D., F.A.C.S., Professor of Obstetrics, Harvard Medical School; Obstetrician-in-Chief, Boston Lying-In Hospital. Pp. 402; illustrated. Boston: Little, Brown & Co., 1941. Price, \$5.00.

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The Work of the Kidneys. A Guide for Use with the Instructional Sound Film "The Work of the Kidneys." Pp. 26; 6 illustrations. *Control of Body Temperature.* A guide for Use with the Instructional Sound Film "Control of Body Temperature." Pp. 25; 5 illustrations. Prepared by MELVIN BRODSHAUG, Erpi Classroom Films, Inc., and HELEN HAGGERTY, Hunter College, in Collaboration with A. J. CARLSON, H. G. SWANN and F. J. MULLIN, The University of Chicago. Chicago: The University of Chicago Press, 1941. Price, 15c each.

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PROGRESS OF MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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MILITARY OTOLARYNGOLOGY.

A SIGNIFICANT trend can be detected in the content of many scientific journals. Since the fall of 1939 the march of military events has accented the surgical treatment of such basic problems as compound fractures, shell wounds, bullet injuries, blood transfusion—to mention but a few. Nor have the military aspects of oto-rhino-laryngology been overlooked. Though the American literature has treated the field but sparingly, it appears fairly certain that with a heightening of the world crisis an increasing number of articles will appear therein. Meanwhile, the American reader must rely mainly on reports from abroad.

Dickson and his associates⁷ deal with the effects of airplane engine noise on the auditory acuity of aviators who have been subjected to it without protection for the ears. All observations were made with a pure tone audiometer. At first the loss is temporary, but it gradually becomes permanent. Deafness may not be noticed by the individual until the speech-hearing frequencies are involved. Bone and air conduction show a parallel loss. Though this loss is in the high tone range, wave analysis of aircraft noises shows that all the components of large amplitude are of low frequency. Thus it appears that a low tone noise is producing a high tone deafness. Protection of the ears diminishes the danger and different methods of protection are being tried. At present the flying helmet with close-fitting telephone receivers seems the most effective means of protection. In a discussion of gun fire deafness Passe¹⁵ finds that naval personnel exposed to gun fire of 3, 4, and especially 4.7 inch caliber, if not operating in enclosed turrets, are subject to deafness. In more than half the cases observed, cotton-wool plugs were the only means adopted for protecting the ears. Deafness and tinnitus lasting for variable periods were complained of, and at times rupture of the tympanic membrane occurred. Though not always

complete, recovery invariably resulted, and the tinnitus subsided. The upper register in the audiofrequency scale was the last to recover. Craig⁴ describes 6 cases of injury to the tympanic membrane caused in the present war by rifle fire, field gun fire, or bombing. None of the patients had worn any protectors and none had received any treatment until they arrived in the hospital, 1 to 9 days after the injury. Two of the cases seen within 24 hours did not develop otitis media and healed quickly; only 1 patient complained of pain, and that at the time of the explosion; no patient complained of giddiness. Wilhelm²⁰ finds that the ear is the organ most sensitive to the effects of vibrations and sudden variations of pressure, and consequently the most susceptible to sudden changes in the surrounding air. Such changes of pressure and degrees of intense noise are encountered by aviators, gunners, divers and the personnel of submarines. These differences of pressure and noise intensity are capable of producing tympanic and labyrinthine symptoms such as deafness, vomiting, disturbances of equilibrium and loss of consciousness. These at times are only transitory, but at others extremely dangerous. Campbell and Hargreaves² classify deafness of aviators according to the following causes: acute fatigue of the end organ of hearing and related structures; chronic accumulative fatigue of the end organ and related structures; conductive deafness due to changes in pressure in the middle ear; and chronic conductive deafness due to alteration in tissue resulting from faulty ventilation of the middle ear.

In the first World War 50% of those who died on the battlefield had been shot in the head or neck. Of the casualties passing through first-aid posts, 15% are head injuries, and by far their greatest risk is infection. According to Olivecrona,¹⁴ partial or incomplete operative treatment of the wound does more harm than good. Early removal of foreign bodies and necrotic tissue is indicated, but it should not be attempted until the patient is in a hospital fully equipped for brain operations. Money¹³ favors segregation of those with head injuries under the care of special teams. By as complete a removal of damaged tissues and foreign bodies as possible the prevention of sepsis can be hoped for with early operation. In penetrating injuries, if operation is delayed more than 24 hours, the death rate is much higher. Peiper¹⁶ opposes operations on head injuries in or behind the front line. First-aid treatment should include removal of the hair and application of iodine to the scalp. To fix the bandage, two splints are applied, one from shoulder to shoulder, and the other from the middle of the back to the top of the head. The presence of neurologic signs is no indication for operation unless they are due to progressive compression. Otherwise the only indication for operation is to check infection. Splinters of bone are more likely to give rise to abscess than metal. Even the smallest wound on the scalp has to be carefully examined as early as possible. A severe depressed fracture may be hidden beneath a small wound, with or without injury to the brain.

Early local cleansing and loose suture of all facial wounds is advocated by Davis.⁵ Wounds involving frontal sinuses and orbital and ethmoid regions are likely to be complicated by extensive fractures of the anterior fossa. This frequently leads to meningitis or intradural hemorrhage. Free drainage must be instituted very early. Bullet wounds through the antrum seldom need treatment. When the mandible is

fractured, teeth in the fracture line must be removed and fixation applied. Maxillo-facial injuries in war are described by James,¹² Axhausen,¹ Hautant¹¹ and Pichler.¹⁷ The rôle of plastic surgery in injuries of the face is stressed by von Wedel¹⁸ who maintains that repair of all soft tissue injuries should be early if possible, with thorough examination of injured parts, complete hemostasis, and accurate re-suture of all layers. Thorough débridement under general anesthesia is essential in all wounds containing dirt. In facial fractures, other than jaw fractures, the first principle is never to remove any piece of bone; if it is loose, replace it and allow it to act as a bone graft. Replacement of fractured malar by the upper buccal sulcus route is advocated. The advantages of interdental wiring as a means of obtaining immediate immobilization of fractured mandibles is advanced by Walker.¹⁹ The greatest utility is claimed for labial arch wiring. The advantages of this method are: where teeth are missing, the gaps can be bridged with the arch wire, traction can be applied in the right direction, and elastics can be used to effect a complete immobilization or a gradual reduction. This method is not advocated as a permanent fixation where there is a considerable loss of tissue. In commenting on war injuries of the jaws and face, Cole³ believes that segregation of patients encourages specialized treatment and nursing while at the same time it has a beneficial psychologic effect on patients suffering from similar disabilities. The restoration of function is much more important than cosmetic considerations, and therefore the bony lesions should be dealt with first.

Wounds of the larynx are rare in modern warfare, not more than 3 per 1000 cases, but they are usually extremely serious when they do occur. In a large lesion of the laryngeal cavity first-aid consists in stopping hemorrhage and keeping the respiratory passages clear. Tracheotomy should always be carried out as soon as possible. Despons⁶ emphasizes the importance of doing low tracheotomy under local anesthesia in injuries of the larynx, even when there is no open wound. Freud⁹ calls attention to the effect on the voice of wounds of the lung and of the trachea, as well as of the larynx. Even when the vocal cords are injured it is possible by reëducative exercises to improve the voice, adapting the voice production and the breathing to the pathologic condition present. It is suggested that there should be special clinics for such individuals. According to Falk,⁸ all injuries of the larynx should be regarded as surgical emergencies, and stretcher-bearers should be taught to prevent the wounded man from speaking. If dyspnea is a prominent symptom the patient should be carried with the head bent backwards, since this causes pressure of the larynx against the cervical spine and not only makes breathing easier, by widening the airway, but also helps to control bleeding by compression. In many cases it will be uncertain whether the esophagus is injured or not, and until this point is established, food and drink should be avoided, and the patient given rectal salines to prevent dehydration.

In view of its possible increased incidence in war time, Gissane and Rank¹⁰ report a case of post-traumatic cerebrospinal rhinorrhea, successfully treated by operation. They conclude that a distinction between early and late onset of this condition is important with regard to prognosis and treatment. In the early type, which is apparent im-

mediately with severe head injuries, there is a tendency for spontaneous recovery if the patient survives the initial head injury. The delayed type occurs when the patient appears to have recovered from the initial head injury. For this group operation is indicated. In the case described by the authors a free graft of periosteum was placed over the roof of the frontal sinus to occlude the defect.

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NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

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THE LITERATURE ON MILITARY PSYCHIATRY SINCE 1938.*

In order to understand how psychiatry might help expected socio-economic disruptions, a fairly comprehensive survey was begun in 1938 of the available literature on the problems of psychiatry during the years 1914 to 1919 and on military psychiatry during subsequent years. In view of the events of the last 2 years, the author has attempted an interpretative review of the literature on Military Psychiatry.

The literature on military psychiatry since 1914, if sorted chronologically, falls easily into four periods, namely:

- I: 1914 to 1919.
- II: 1919 to 1929.
- III: 1929 to 1938-39.
- IV: 1938-39 to 1941.

* From the Psychiatric Liaison Department which is a division of the Department of Psychiatry of the University of Colorado School of Medicine and Hospitals, made possible by a Rockefeller Fund Grant.

PERIOD I (1914-1919). The literature of this period graphically depicts how psychiatry was then far less advanced than it is today and well isolated from the accepted fields of medicine, but well aware of the need to develop more of a genetic-dynamic understanding of mental ill-health and especially better therapeutic procedures. The literature shows how psychiatry arose to the demands of the armed services that their personnel be chosen more adequately in terms of personality competency, that steps be taken to preserve its mental health and to treat psychiatric casualties more effectually. The results of the labors of the few trained psychiatrists available at the time in surveying the situation, starting the education of the public in mental hygiene, formulating plans of procedure and following through those plans were truly amazing and productive. Psychiatry began to emerge from its isolation and gradually became recognized as an important branch of medicine. Mere custodial care of patients began to be replaced by active treatment and interest in research was stimulated.

PERIOD II. The literature on military psychiatry between 1919 to 1929 is characterized by reminiscences of the experiences of Period I, and lamentations that more could not have been done to prevent the staggering problem with which the country and medicine was faced in Period II in the form of psychiatrically disabled ex-service men. The literature of this era indicates furthermore that little, if any, specific planning was undertaken for a future emergency involving large numbers of psychiatric problems and shows a gradual diminution in any reference to military psychiatry, *per se*.

PERIOD III (1929 to 1938-39). The literature on military psychiatry during this interval is characterized by the absence of any significant writing on this specific subject, except occasional reports from the Veterans' Administration.

PERIOD IV (1938-39 to 1941). The literature of these years illustrates to some extent a repetition of the circumstances in which psychiatry found itself in the first period. Psychiatrists with far more knowledge of personality disorders, better techniques for diagnosis and improved therapeutic procedure, are now hurrying to formulate plans to meet the demands of the present crisis, realizing that a task of public education bigger than ever before lies ahead and that the need exists for long-term planning.

The general status, special problems and aspects of military psychiatry of the above first three periods and part of the fourth have been very adequately reviewed in Miller's recent book, "The Neuroses in War."²⁶ This book contains a comprehensive bibliography to the current literature of those times. Volume 10 (Neuropsychiatry) of "The Medical Department of the U. S. Army in the World War"²⁵ offers a very full account of the military psychiatric experiences of the U. S. Army during the first period. Since these books are available and practically no other writings of importance are to be found between 1929 and 1938, the remainder of this paper will be devoted essentially to a review of the current literature of the last 3 years dealing with military psychiatry. This will be done by arbitrarily grouping the material under several headings.

Incidence of Psychiatric Disorders—A Challenge. Many of the data dealing with the incidence of psychopathy among the personnel of the

armed forces during the last 3 years are but reiterations of those noted in earlier writings^{25,26} on military psychiatry. They are noted here again for the purpose of orientation as to the magnitude of the problems now facing the medical profession.

In a recent paper Bowman⁶ stated that one-half of the discharges from the English Army in 1917 were for neuropsychiatric conditions, and, excepting the actually wounded, one-third of all discharges were for personality disorders. Along this same line, this author points out that in the United States during World War I, 2% of the recruits and selectees were excluded from the Service, and, after induction, 3% more were discharged on account of neuropsychiatric disorders. It has been stated elsewhere² that in the United States in 1917, when few psychiatric facilities were available, 0.477% of the males of conscript age were rejected by draft boards because of "mental and nervous" difficulties.

According to Davidson,¹³ 3% of those inducted into the U. S. Army in World War I were found to be "mentally defective." Of the soldiers sent to France, 3000 were found, after their arrival there, to be "imbeciles, paretics, epileptics and other types of psychopaths" and therefore not qualified for service. There were undoubtedly many more cases not apprehended. It has been estimated that 90% of the chronic war neuroses were discharged from the service undiagnosed and untreated.^{20a}

Despite the many advances made in mental hygiene, psychiatric diagnosis, and in the psychiatric education of physicians, a great problem still faces us. In 1937, in a Naval Training Station in the United States, of 5578 recruits received for training over 1% were hospitalized before their training was completed for conditions which were existent before their enlistment and which were not aggravated by the naval service. Of this group of cases, over 45% were psychiatric disorders.³⁵ A statistical study²¹ of several foreign units (Sweden, Belgium, Holland, Finland, Estonia, Poland, Germany) showed that 1% of all conscripts examined were rejected because of psychiatric conditions.

The problem does not consist merely in the maintenance of the efficiency of the armed forces at a given time. Social, economic and public health issues are also involved. Of the 54,117 ex-service men hospitalized by the Veterans' Administration,¹ approximately 60% were hospitalized because of neuropsychiatric disorders. Two out of every 5 veterans are receiving pensions because of neuropsychiatric conditions; and of every 5 veterans receiving compensation for service-connected disability, 1 is psychiatrically disabled by personality difficulties other than those accounted for by mental deficiency, psychopathic personality, chronic alcoholism, and paresis.² Since World War I, the Veterans' Administration is said to have spent one billion dollars⁶ on claimants who have mental and nervous troubles stemming from their military services in World War I.

As of the last part of April, 1941, figures regarding the Selective Service rejections in the United States indicate that 6.2% were on account of "mental and nervous" disorders. This figure speaks well for the improved efficiency of American psychiatry in medical education and in rising to the present emergency to prevent some of the costly problems mentioned above. However, the unearthing of these cases

connotes an additional problem that must be met, namely, the follow-up guidance and treatment of these cases and the attempt at readjusting them more effectively to some useful form of civilian life.

The Psychopathology of Military Life. THE MAJOR PSYCHOSES. The literature of the past 3 years dealing with the psychopathology of military psychiatric casualties has to date given practically no space to the major psychoses other than to stress that the reactions are essentially the same as found in civilian life, that the treatment is likewise similar, and that all such cases should be eliminated from the service as soon as possible. The only exceptions to this trend noted by the author have been two papers, one dealing with depressive reactions and the other with very severe "support disorders."

Curran and Mallinson,¹² in a recent paper, point out that the evidence of "certifiable insanity" has not greatly increased in the Royal Navy as a result of war, but that the incidence of depressions in the Royal Navy personnel equalled that of hysteria (13 % of psychiatric casualties). They suggest that the diagnosis of depression has been avoided because it connoted a major psychosis. The study of Curran and Mallinson was made on 44 cases which they felt presented primary mood disorders of the depressive type. These authors stated that depressive reactions were inclined to occur in "excellent men, who finally broke down, not through any deficiency in morale, but largely owing to certain deficiencies in adaptability due to a number of causes," such as: "age, temperament, quite a high proportion of mental backwardness or arteriosclerosis." Family history and domestic adversity seemed to be of little significance. The presence of hypochondriasis in the reactions was of little apparent prognostic importance. Most cases were said to have shown some hysterical coloring. Of all the cases, 28 % were returned to duty, "26 % showed on discharge any significant reduction in their previous social capacity and not more than 5 cases needed further hospital care." The average stay in hospital for these cases was 3 months. The percentage of officers returned to duty was high (a small series—8 out of 13). Good intelligence, personality plasticity, "rapid reactivity" and an illness lasting less than 6 months were favorable to a good prognosis. The early appearance of hysterical reactions tended to prolong the depressions and the more of this coloring the less likely the possibility of returning the patient to duty. Curran and Mallinson emphasize that the treatment of these depressive reactions is the same as in civilian life, that it is useless to attempt to "keep affective states in the firing line" and that in the treatment of these depressed "war cases," the "proportion of firmness to sympathy should vary in direct relation to the hysteria present."

In contrast to the psychiatric reactions that occurred in the British Army personnel not actively fighting in France (1939-1940) and who "would be expected to react according to their history of instability," Sargent and Slater³⁰ described a "new type" of reaction, an "acute neurosis" that appeared during the Battle of Dunkerque. These reactions, according to the authors, were inclined to occur in men who had previously shown a good work record, normal personality development and performance, satisfactory adjustment to army life, and were of normal intelligence. The soldiers on meeting such factors as bodily danger, continuous exertion, loss of sleep, inadequate food eaten irregu-

larly, intermittent but perpetual shelling, sight of comrades and civilians killed, and the continuous retreat without the possibility of retaliation, finally, after varying periods of time complained of "acute anxiety," insomnia or terrifying dreams when they did sleep, "inner unrest," and of being startled by noises. Objectively, these patients showed signs of exhaustion and appeared either tense and anxious or listless and apathetic. Their faces were immobile and this, along with the coarse, irregular tremor of the hands ("sometimes resembling that of an extrapyramidal lesion except in that the tremor could be controlled" momentarily) caused them, at first glance, to simulate the picture of Parkinsonism. In some there was nystagmus. These men were easily startled by noises, especially by those of airplanes, commonly showed an amnesia for the worst part of their experiences and manifested "many hysterical features such as confusion, fits, hallucinations," and so on. "With minimum treatment progress was towards improvement."

THE PSYCHONEUROSES. Lord Horder¹⁷ was of the opinion that war produces no new type of personality disorders. He has outlined three classes of "neuroses": 1, "general concussion reactions" in men without visible wounds (5% to 10%); 2, "emotional shock" reactions (80% of cases) occurring either as "acute reactions in men with a predisposition" or slowly developing in others "as a result of prolonged strain and terrifying experiences often precipitated by some trivial experience; and 3, nervous and mental exhaustion as a result of prolonged strain and hardship." This authority states that in the "chronic cases of war neuroses" there exists a "congenital or acquired predisposition to excessive and therefore pathological reaction."

Hurst,¹⁹ in an article in 1939, reviewed his experience with psychiatric disorders of World War I and compared them to those of civil life. He indicates that exhaustion and emotional strain are the two factors that account for a greater incidence of "neuroses" in men during war-time as compared with peace-time. Exhaustion, he points out, occurs in the setting of forced marching, strenuous fighting, and temperature changes. The added emotional strain occurs in the setting of bombardment, fighting, and conflict arising from participation in fighting. Hurst explains that these two factors lead to neurasthenic reactions that are more severe than those of civilian life, hysterical and obsessive-compulsive disorders, and also aggravate any incipient organic nervous system disease. The second or emotional factor, according to this clinician, may cause "functional hyperadrenalism and hyperthyroid states." "Terrifying experiences," he says "increase the susceptibility to suggestion, especially if physical injury occurs in association with the experience." In his paper, Hurst goes on to review some of the more common hysterical sequelæ to gassing, concussion, wounds, and so on.

In a recent article on aviation medicine, Ceres¹⁰ indicates some of the psychiatric needs of aviation medicine. In his opinion, "fifty percent of the crashes in aviation can be attributed to the fault of the pilot—especially memory and attention difficulties and poor judgment." He discusses some of the psychiatric factors in high altitude and speed flying and, by implication, stresses the importance of evaluating the personality of aviators.

The Psychopathologic Effect of War on Civilian Populations. The first two works referred^{25,26} to elucidate the very few available facts about civilian psychiatric reactions to warfare up to the summer of 1940. Since then the literature dealing with this subject has been scant. Since the summer of 1940, articles in languages other than English have been few and these smacked a little too much of propaganda and cautious writing on account of censorship to make evaluation by this author tenable. The English literature considering civilian reactions has as yet not brought out any new disorders as compared with World War I, and in the main indicates that about the same type of reactions have been precipitated in the two wars. So far as this author has been able to learn no factual statistics have been reported as to the number of civilian psychiatric casualties.

ADULTS. Stalker,³¹ in June, 1940, indicated that at that time civilian panic states, marked enough to require hospital care, were few in number. He was inclined to believe that those that did arise occurred in people who were already psychiatrically sick. Boldie⁴ has stated that, in the recent war, crimes of violence and even delinquency have diminished.

Pegge,^{28a} in October, 1939, reviewed his experience with the psychiatric casualties that were admitted to his hospital during the first days of war. He reported a variety of conditions, not unlike the disorders of peace-time civilian life, that were precipitated by fear. According to Pegge, the fear of air raids that did not materialize constituted the chief strain, and in only a few cases did the air raid sirens act as the actual stimuli. The victims in general "were intelligent and of the educated classes."

One year later this same author^{28b} analyzed the psychiatric casualties coming to the same institution from the civilian ranks. By this time most of the people had "become accustomed to air raid warnings and many psychiatric cases had been evacuated from the population." Of the 29 casualties studied, some were World War I "neurotics" who broke down under the strain of the times, but the majority were those who reacted psychopathologically when in actual danger or were knocked down by bomb blasts, and so on. Of the 29 cases, 13 gave no historical evidence of previous neurotic or psychotic tendencies. Five patients did give a history of previous personality difficulty and 2 "concussed" patients refused examination. He concluded that at least 17 of the 29 cases could be attributed to war stress. Most of these patients were hospitalized direct from bombed areas. They showed "varying degrees of disturbed consciousness—often amnesia." Coarse, generalized tremors, easily exaggerated by gun fire, were commonly shown by them. Besides, they often manifested "uncontrollable emotional behavior with weeping." Only 1 patient showed an hysterical reaction and "that was an old case" of hysteria.

Rosenburg and Guttman²⁹ have reported an interesting study made on 103 "chronic" psychiatric patients who had attended Maudsley Clinic for at least 1 year prior to September, 1939. They found that the patients with obsessive-compulsive reactions, the "chronic hysterics" and the hypochondriacs were relatively unaffected by the outbreak of the war, and subsequently needed no more attention than they had previously. On the other hand, the anxious and depressed

patients were adversely affected in that they tended to become more acutely ill.

The factors instrumental in bringing about psychiatric disorders in civilians exposed to the conditions of war have been variously listed by several authors.^{4,5,26,27,32,37a,b,c} The following is a summary of these:

1. Fear due to:
 - (a) Risk of attack or injury;
 - (b) Economic change;
 - (c) Threat of family separation;
 - (d) Threat of food shortage;
 - (e) Threat of deprivation of luxuries and pleasures.
2. Declination of individualism and increase in mass psychologic reactions such as anxiety.
3. Insufficient nutrition.
4. Inadequate rest.
5. Difficulty in maintaining social and personal hygiene.
6. Interference with occupational efficiency.
7. Evacuation to new surroundings.

CHILDREN. Although, as referred to above, one report⁴ from England indicates that the incidence of delinquency among children has decreased since the outbreak of war, a review of the literature other than psychiatric and medical would seem to indicate that it probably has not done so, at least in the larger cities. The milder delinquency problems that in peace-time would be attended to are more or less trivial in war-time. Most of the papers dealing with the problems of childhood associated with the conditions of war in England indicate that "child neuroses" are greater in evacuees than those who remain at home with their parents.^{4,14,34}

Other factors leading to behavior disorders in the children are: insecurity in a new environment, repercussion to adult strain, direct air raid experience, foster parents ignorant in child management, change in schools, indiscriminate and inadequate billeting, and return of the mother to the former home leaving the child behind. From the literature it seems that the child showing a reaction to bombing is easily and successfully treated, while the one reacting to a broken home is very difficult to clear. One author¹⁴ interestingly noted that over three-fourths of the children showing behavior disorders were between the ages of 7½ and 11½ years. The diagnostic and age incidence of the reactions ran practically the same as has been noted in the psychiatric referrals from a pediatric clinic in a large inland American hospital.^{3b} It is felt, therefore, that the type of reaction and the age at which it occurs are not significant insofar as war is concerned. If the experiences of peace-time hold true, then this author feels that some of the later reactions of life stem from prolonged strain with anxiety and the adverse emotional tendencies, disturbed habits, and so on, in childhood. In view of this, it is more than a likelihood that more adult disorders can be expected in the future, especially if civilian populations continue to be subjected to the stresses of modern warfare for a long period of time.

Prevention. How to prevent even most of the psychiatric disorders of the personnel of the armed forces cannot be solved during a critical period such as now. A practical answer will be forthcoming if psychiatry and medical education in general do not lapse into as much of a state of inertia in regard to military and industrial medicine as they

did in 1919 to 1939, following World War I. Of course, too, in setting forth upon such a program, it probably is worth bearing in mind that it might not be practical to exclude all moderately unstable men from the service, since many of them, under certain exigencies have, are, and will continue to perform their duties with efficiency and valor.

Gordon¹⁸ suggests that all physicians eventually should be given the means by which they can evaluate the strain to which a person is subjected and the amount of stress an individual can tolerate without "breaking" in order that prevention of psychopathic episodes can be augmented. Others,^{7,11,13,17,24,33} in discussing prevention of personality disorders have made the following recommendations:

1. Every examining board physician and individual officer should have a knowledge of personality disorders and be encouraged to use it.
2. All recruits and selectees should be drafted for a period of probational training of 3 to 6 months, in order that the misfits, neurotics, psychopaths and psychotics can be eliminated.
3. Departments should be developed to form a liaison between school and community agencies and other services so that educational, social and health records of the recruits and selectees can be made more easily available in evaluating the men before induction.
4. Group psychometric tests should be done on all men before induction.
5. Armed services should, as far as it is feasible and possible, avail themselves of the experiences and techniques of industry in choosing personnel.
6. There should be one psychiatrist, or physician with some psychiatric knowledge on each county draft board—at least on each of the larger county draft boards.

Lord Horder¹⁷ has advised that in order to prevent many of the psychiatric problems of war, the following should be instituted:

1. Education of the public (*a*) in the fundamentals of personality functioning and the disorders thereof; (*b*) in the realization that a "neurosis," no matter what the cause, is not to be considered a battle casualty and that psychiatric illness cannot, *per se*, be a basis for honorable discharge from the service.
2. More attention to eliminating poor sanitation, bad housing accommodations, and abuse of alcohol, drugs, and so on.
3. More attention to the dietary of the populace, especially of the soldier.
4. Control of venereal disease.
5. Elimination from medical and psychiatric terminology of such terms as "shell shock," disordered action of the heart (D. A. H.), neurocirculatory asthenia, and all others that implicate a part of the body as being diseased when it is only participating in a personality reaction.

Besides the foregoing, this author would like to suggest that the following additional preventive measures be considered:

- (a) Instructing the public in mental health through a wider propagation of *facts* than now prevails and more attention to improving laws dealing with the mentally sick.
- (b) Existing agencies should be made use of or new ones established to advise and assist rejectees in making better civilian adjustments and in obtaining medical and psychiatric treatment.
- (c) Rehabilitation and vocational guidance services should be set up to reestablish disabled and discharged service men in society in a useful way.
- (d) Development of more or less permanent organizations to formulate means of improving case records, to evaluate the clinical and other data, to direct research and to integrate those data with new medico-psychiatric movements and projects that are of particular importance to both military and civil mental health.
- (e) Future maintenance of interest and active work in the field of military, industrial and vocational psychiatry.

Prognosis. "The prognosis as to the recovery of a psychiatrically ill soldier or officer sufficient to permit his return to active service is, in

the light of present knowledge, rather difficult to evaluate since very few statistics are available. Certainly several factors are always operative and have to be considered in any such prognostication. These are: the age of the disabled soldier or officer, his intellectual level, his pre-army and pre-war social adjustment and behavior, the conditions under which the personality disorder developed, the nature and duration of the psychopathologic reaction and the circumstances under which treatment is administered.

"It goes without question that those individuals unable to adjust to army life and to function efficiently by the time the first half of the indoctrination period has passed, will never be able to do so, and, therefore should be eliminated from the service. If the need for man power is compelling and the local situation permits, many men of relatively low intelligence but of stable temperament, some with minimal psychopathic trends, a few "stationary" organics or those amenable to treatment, a few mildly depressed soldiers, and many of the psychoneurotics, frequently can be allocated duties that are either simple, or offer little strain and are within the capacity of the particular soldier. Discussion of the soldier's personal problems in terms of special considerations by medical and line officers will avert many actual breakdowns and will work toward increasing the morale and efficiency of the respective units.

"Experience in the World War I seems to indicate that once a soldier, in the service, develops a major psychosis, excepting a delirium, the chances are very poor for rehabilitating him sufficiently for return to active duty. The psychotic soldier should, therefore, be evacuated and as soon as feasible eliminated from the service.

"In the instance of psychoneurotic developments, especially during the pre-engagement and combat periods, prognosis is likewise variable. However, the psychiatric experiences of the World War I, and subsequently, indicate that the expected outcome of adequately treated psychoneurotic reaction types with onset in the combat zone will be about as follows:

Exhaustion and fatigue states	} Possibility of an officer or soldier returning to active duty decreasing from above downward
Concussive reactions without central nervous system injury	
Hypermotility states	
"Gas neurosis"	
Conversion-hysterical states	
Anxiety states and "anticipation neuroses"	
Obsessive and compulsive reactions	
Hypochondriases	
Tension and irritable weakness reactions	

"It is estimated that about 25 % to 30 % of the psychiatrically disabled officers and approximately 55 % to 65 % of the privates and non-commissioned officers will be able to return to full active duty after a psychoneurotic episode.

"It is to be expected that the farther from the site of the inception of the disorders, especially the psychoneurotic ones, that treatment is instituted, the less the expectancy for recovery. This is particularly true during the combat period."^{3a}

The prognosis is poor for returning an officer or soldier to full and active duty if he develops a psychoneurosis or psychosis while on furlough or "leave."

If a soldier is incapable of returning to active service, the facilities of the various social agencies should be utilized, when advisable, in steering him into some constructive work as a civilian.^{3a, 8, 11, 16, 20b, 22, 23, 25, 26}

The average physician is often inclined to procrastinate about committing himself as to the essential negativity of organs that participate in the various psychopathologic states. As has been alluded to previously, the result is that the psychiatrically ill soldier is made too body conscious and thereby invalidated. For this reason the British authorities¹⁷ have advised against such practice. For example, Whishaw³⁹ studied 250 invalidated ex-soldiers of World War I, 20 years after the onset of their disability. Of these men, 156 (62%) had carried the diagnosis of "D.A.H. or psychoneurosis" for 20 years; 130 of them had "D.A.H." Of these 130 men, 126 were found to have normal hearts in 1939. Two of the remaining 4 had developed hypertensive heart disease, 1 chronic nephritis and 1 rheumatic heart disease subsequent to their war service. Of these 130 ex-soldiers, 35% still considered themselves totally disabled and all were heart conscious.

Treatment. Even to summarize the treatment of the psychopathologic states of war-time would require space far beyond the limits of this paper. Miller²⁶ and Kardiner^{20b} have done this exceedingly well in their respective texts. Since the therapy of war-time disorders is essentially that of peace-time, the standard texts on psychiatry can be referred to. The review to follow is based entirely on some of the more pertinent current literature, read by the author during the last 3 years.

The history of psychiatry in the World War I^{25, 33} proved that intelligent handling of psychiatric problems increased the percentage of recoveries, improved the morale of the forces and increased their general efficiency. Mayer-Gross²⁴ has outlined what war-time psychiatry should do to be of full service. The points he emphasized follow:

1. Making it possible for recruiting and medical officers to consult psychiatrists in all doubtful cases.
2. Psychiatric consultation should be available in all general and base hospitals.
3. Special psychiatric units of general hospitals or psychiatric hospitals should be easily available.
4. All acute "neuroses" should be treated in or as near as possible to the combat area.
5. As many as possible of the "neurotics" returned to the Zone of the Interior should be rehabilitated in civilian ranks.
6. All surgical cases "with non-penetrating or penetrating head wounds should be treated psychologically and educationally as well as surgically."
7. Civilian understanding of personality problems should be improved.

Several British psychiatrists,^{15, 30} basing their conclusions on therapeutic experiences with 1500 cases, state that "radical treatment is out of the question." They attempt to handle the patient's symptoms, improve his general health, and by history-taking and interviews with the patient under the influence of hypnotics use suggestion and desensitization to return him to his "pre-breakdown" condition. Their objective is to return the patient quickly to active duty, or to outline procedures for his readjustment to a socially valuable life. These authors point out that one of the difficulties in treating the military psychiatric casualty is to be found in what ultimate recovery may mean to the patient. In civilian life "the reward for getting well is greater freedom from hampering difficulties." In the military case,

"the reward is the privilege of returning to the scene of his failure with the knowledge that he has failed." Debenham and his confrères caution against the therapist being too optimistic and not "invaliding" casualties quickly enough.

As to the handling of "violent and suicidal patients," Weatherby³⁶ gives good advice, similar to that to be found in the standard textbooks on psychiatry.

In treating the civilian panic and confusion states, concurrent with the bombing of Britain, referred to previously under the heading of *psychopathology*, Pegge^{28b} used the following procedure: The patient is seen and examined as soon as possible. If he is not conscious, he is treated as though hypnotized; that is, he is given reassurance specific to the use of disturbed functions, explanation is made of the mechanism of symptom formation, the patient is commanded to open his eyes and give his name and address. If the patient is excited and disoriented, he is given a hypnotic drug (after explanation) and suggestions are carried out as before. All cases are seen on the second day and the treatment procedure repeated. If the patient has not recovered in hospital within 3 days he is sent to a psychiatric hospital. Of the 29 cases reported, 6 were successfully treated in the out-patient clinic and 10 in the hospital within 3 days. Eleven were referred to psychiatric hospital, 1 was sent to a "psychiatric observation ward" and 1 refused treatment.

In a study of the anxiety of civilians concomitant with the "war of nerves" and the bombing of cities, one author⁴ fears that if treatment is not efficient, there is possibility of many affected civilians developing "hiding and shelter habits," panics, compulsive disorders and "neurotic disabilities."

Cameron⁹ emphasizes the value of occupational therapy in treating the psychiatric casualties of war. He advises that an occupational therapy department should be an integral part of every hospital and it should be under the direction and control of a medical officer. The work should naturally be useful and varied, prescribed specifically for the individual and should be regarded as treatment.

Conclusions. Perusal of the literature shown in the bibliography indicates that nearly all of the writers, besides reporting details of their experiences and techniques, have made a plea that psychiatry keep to the middle of the road, improve more rapidly the courses in psychiatry for medical students, develop facilities whereby all medical officers can have instruction in the principles of personality functioning and the diagnosis and treatment of the disorders thereof, give attention to improving compensation laws, stimulate the public to organize adequate facilities to readjust the rejectee, the discharged and invalided men of the services, present more facts to the public at large in regard to the disorders of personality, and correlate the researches of the many allied fields of science that have a bearing on psychiatric medicine.

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PHYSIOLOGY.

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF APRIL 15, 1941.

On the Phosphorylation Hypothesis of Glucose Absorption, With Special Reference to Phlorizin. LYLE VIBERT BECK (Department of Physiology, Hahnemann Medical College). The finding by Kalekar (*Enzymologia*, **2**, 47, 1937) that low concentrations of phlorizin inhibit the phosphorylation of hexoses by rabbit kidney brein has been confirmed. Phlorhizin also markedly inhibits the acid phosphatase of rat kidney cortex and intestinal mucosa, while having little effect on the corresponding alkaline phosphatases.

Combined barium precipitation—N.HCl hydrolysis experiments indicate that the increase in organic phosphate produced in the intestinal mucosa of rats by giving them glucose by stomach tube (*cf.* Laszt and Sullmann, *Biochem. Ztschr.*, **278**, 401, 1935) is due to increase in concentration of a number of organic phosphate compounds. The considerable increase in the 0-7' (minute) N.HCl fraction is apparently largely due to formation of adenylypyrophosphate, since this fraction was found mainly in the Ba precipitate fraction. Increases in the 7-180' N.HCl fraction and in the difficultly hydrolyzable fraction (not hydrolyzed in 180' by N.HCl) are due chiefly to formation of carbohydrate-phosphate compounds, since these fractions were found mainly in the Ba soluble fraction.

Using the method of Cori, Colowick and Cori (*J. Biol. Chem.*, **121**, 465, 1937), no change in concentration of either glucose-1-PO₄ or phosphoglycerate in the intestinal mucosa was found on giving glucose. Under these same conditions an increase in concentration of compounds giving the Seliwanoff fructose reaction (Roe, *J. Biol. Chem.*, **107**, 15, 1934) occurred.

M/50 phlorizin does not affect the increase in the 0-7' N.HCl (pyrophosphate) fraction produced by 5.5 % glucose, but definitely diminishes the increases otherwise produced in the 7-180' fraction and in the difficultly hydrolyzable fraction (phosphoglyceric acid?). The increase in concentration of compounds giving the fructose reaction when glucose is given is diminished in the presence of M/50 phlorizin.

While the above findings may be interpreted as indicating that phosphorylation-dephosphorylation processes play a considerable rôle in glucose absorption, they indicate that if this is true the pathways involved are considerably more intricate than a simple phosphorylation and dephosphorylation of the glucose molecule.

The Effect of Brass Rings on Tissue Cultures of the Heart. M. J. HOGUE (Department of Anatomy, University of Pennsylvania). Using a liquid medium which was a combination of Tyrode solution, Locke-Lewis solution and chick embryonic extract, tissue cultures of chick embryo heart, liver, lung, intestine, amnion and skeletal muscle were grown over brass rings sealed to glass slides with salvoline. The controls of the same tissues, in the same medium, were grown over glass depression slides. Further controls were grown in plasma and embryonic extract. The percentage of growth of fibroblasts from the different tissues showed great variations when grown over brass rings, the heart fibroblasts showed the least growth and the lung fibroblasts the most growth.

When good growths of heart fibroblasts were transferred from glass depression slides to slides with brass rings the fibroblasts soon died. Experiments with hypotonic solutions showed that death was not due to a change in the tonicity of the medium.

Since brass is an alloy of copper and zinc, small particles of copper and zinc were placed in the hollow of the depression slides and tissue cultures were inverted over them. Over the copper the fibroblasts grew well, but over the zinc there was little or no growth. Death of the fibroblasts over brass rings and over zinc particles was the same slow process. First there was the appearance of vacuoles around the nucleus, which became pyknotic, then the withdrawal of the cell processes and the contraction of the cell body while small clear blebs appeared over the surface of the cell. Cardiac muscle cells were not as sensitive to the zinc as the cardiac fibroblasts.

The Structure of Bacteria as Shown by the Electron Microscope. STUART MUDD, T. F. ANDERSON, K. POLEVITZKY, and H. E. MORTON (Department of Bacteriology, University of Pennsylvania). Micrographs of bacteria made with the RCA electron microscope have shown very definite differentiation between a solid outer cell wall and an inner fluid or potentially fluid protoplasm. In chains of *Strep. pyogenes* and of aerobic spore-bearing bacilli the continuity of the chain has been shown to be due essentially to the continuity of the outer cell walls. Division in a strain of *Strep. pyogenes* appears to be accomplished by a pinching off of the cell wall and its contained protoplasm. In species of the genus *Bacillus*, intercellular plates, as described by Knaysi and others, may be seen. Disruption of streptococci and bacilli by sonic vibration permits escape of the inner protoplasm, leaving the cell-walls as "ghosts."

Cells of *Mycobacterium tuberculosis* and *Corynebacterium diphtheriae* have been relatively transparent to the electron beam. In tubercle bacilli opaque granular bodies of various sizes may be seen in the inner protoplasm. In diphtheria bacilli grown on blood agar, very striking polar granules are found. In diphtheria bacilli grown on potassium tellurite medium, needle-shaped crystals of metallic tellurium are clearly visible within the cell protoplasm. Shaking such bacterial cells with bromine water dissolves the crystals, a behavior which is to be expected with tellurium metal.

The Liver Glycogen and Lipid Concentration Following Diet and Intravenous Glucose Administration to the Dog and Man in the Presence of Common Duct Obstruction. I. S. RAYDIN, H. M. VARS, JULIUS SCHULTZ, JULIAN JOHNSON, and ELIZABETH THOROGOOD (Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania). It is generally believed that high concentrations of hepatic glycogen protect the liver from many hepatotoxic agents. Regardless of the validity of this impression, it is also widely believed that glucose administered intravenously is the best method of increasing hepatic glycogen. This is untenable except for brief periods of time, since it disregards the calorific requirements of man or animal. We have studied this in the dog in the presence of common duct obstruction.

During voluntary eating animals lost hepatic glycogen and increased liver lipid concentration. When in addition glucose was administered intravenously, the glycogen concentration was maintained and the liver lipid concentration was decreased. Where appetite was stimulated and the dogs also received glucose intravenously, the liver glycogen concentration increased by 84% and the lipid concentration decreased by 25%. Following forced feeding (88 calories per kilo of body weight per day) the liver glycogen concentration increased by 236% and the lipid concentration decreased by 73%. With only a 5% solution of glucose intravenously (50 cc. per kilo of body weight per day) the animal lost 50% of the original liver glycogen concentration.

In man similar data have been obtained. The data from man and dog suggest that if large accumulations of glycogen are desired, these must be obtained by the oral administration of foodstuffs, for such stores cannot be maintained unless the energy requirements are being met.

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